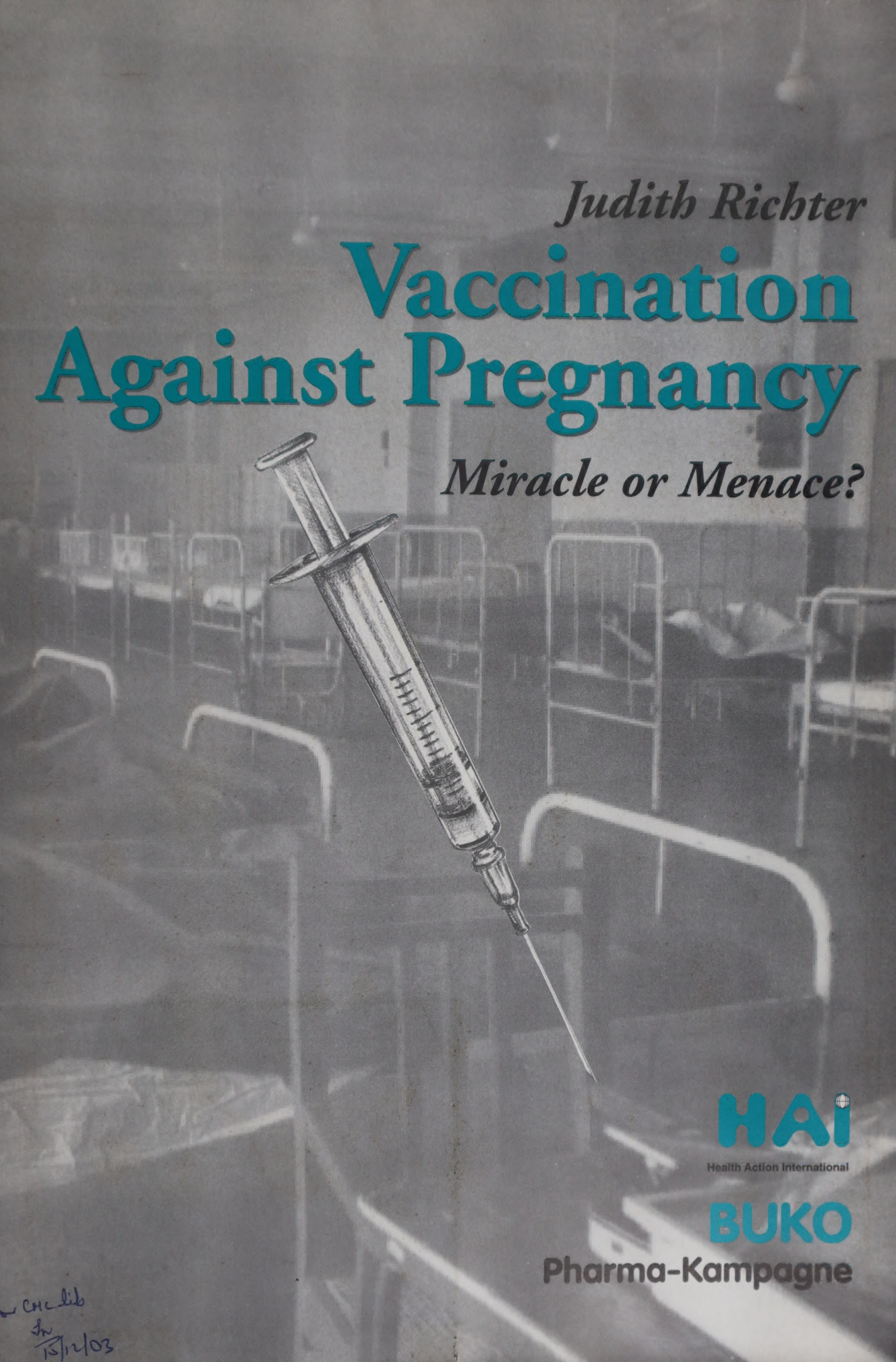
Judith Richter

Vaccination Against Pregnancy

Miracle or Menace?



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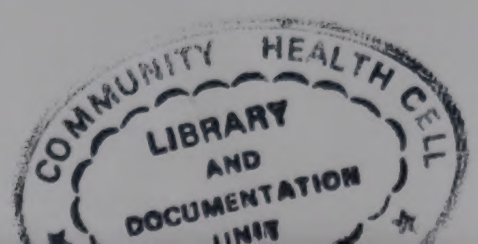

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Judith Richter

INTRODUCTION

"The prospect of regulating fertility by manipulating immune mechanisms has hitherto been a pious hope linking the aspirations of family planners and reproductive immunologists. Now at last the rational and practical application of this exciting yet frustrating tract of science is at hand." (Jones 1982:8)

The idea of developing a vaccine against pregnancy dates from the end of the last century when two immunologists, Landsteiner and Metchnikoff, independently discovered that immune reactions against sperm could lead to infertility. In the 1920s and 1930s, human trials were carried out and an anti-sperm vaccine for women was patented in the United States in 1937. However, it was never marketed, either because of ethical constraints, (Jones 1982:8-10) or because the method was too unreliable (Clarke 1990:45).

After the second World War, research into new contraceptives boomed and many new methods were developed. The development of the contraceptive pill was hailed as giving women freedom from unwanted pregnancies. At the same time, population growth, especially in Third World Countries, began to be perceived as a "population bomb" and a threat to the wealthy North. Extensive provision and administration of contraceptives in Third World countries began to be seen as the solution to the spectre of "uncontrolled" population growth. The United States government, donor agencies, and later on institutions such as the World Bank began directing large amounts of financial aid to population programmes in Third World countries. For example, between 1965 and 1982, the US Agency for International Development (USAID) spent US$ 1.9 billion on family planning programmes. Some of the family planning programmes receiving assistance from international donors relied on coercive practices to convince women to accept contraceptives or sterilisation, such as Bangladesh's sterilisation programme funded by USAID in the mid 1980s (LaCheen 1986:97).

In the 1960s, population oriented non-governmental organisations (NGO's) and the United States government began funding contraceptive research and development. The pharmaceutical industry began to invest less heavily in contraceptive research in the 1970s because of higher research and development costs due to more stringent standards prior to registration. The industry also feared an increase in financial claims from women who experienced adverse effects resulting from a contraceptive (Mastroianni et al. 1990:60). Today, the pharmaceutical industry does little contraceptive research, and this research is mainly directed towards new types of oral contraceptives and new modes of delivery for hormonal methods. Most contraceptive research is done by NGO's, national governments and international agencies.

A major driving force behind contraceptive development since the 1960s has been the aim to limit population growth. New contraceptives are designed to be highly effective, long lasting and independent of the user's whims or abilities. To effectively reduce birth rates, it is assumed that there should be no failures due to improper use or "forgetting to take a pill". Whether or not a woman can stop using a contraceptive any time she wishes has been less of a priority.

Men still have only few options for contraception

Women are still the main target group for contraceptive research. After 40 years of intensive research, men still have only three options for contraception: condoms, withdrawal, or sterilisation. Women must still bear the greatest responsibility for preventing pregnancy and the greatest burden of health risks from adverse effects of contraceptives.

Following several decades in which there was little research on immunological contraception, in the early 1970s advances in immunology gave a new impetus to the idea of a vaccination against pregnancy. The World Health Organization (WHO), the Population Council, the Rockefeller Foundation, the US, the Canadian and the Indian governments all allocated funds for this research.

Many types of immunological contraceptives are being developed. They work by provoking an auto-immune response. They are directed against reproductive hormones, the egg, sperm, or early embryo. Most of these methods are meant for use by women; only two methods are being researched for use in men. Some immunological contraceptives for women have already undergone extensive testing, including clinical trials (testing in humans). Contraceptives directed against the pregnancy hormone human chorionic gonadothrophin (hCG) are at the most advanced stage of research. Several different preparations have been developed by competing research teams.

"The vaccines may prove to be as important a development as the contraceptive pill"

These new contraceptives are being hailed as a breakthrough in immunology and contraceptive research. WHO's task force manager Griffin (1986) said that "the vaccines may prove to be as important a development in birth control technology as the contraceptive pill."

The media and scientific publications have published euphoric articles praising vaccination against pregnancy as *the* solution to the population problem of the South. For example, the views of one of the leading researchers, Pran Talwar from India, are described as follows: "Talwar sees population as an epidemic not unlike the tetanus, diphtheria and smallpox epidemics that once ravaged humankind. And it can be defeated, he declares, the same way by a vaccine... With a vaccine, there would be no remembering to take a pill. No surgery. No struggling with a condom. Pregnancy would be warded off with the same powerful immunological weapons the body uses to fight disease." (Kanigel 1987:26)

Shearman (1982:VII) writes in his foreword to a book on immunological birth control that immunological contraceptives would be an "antigenic weapon" against "the reproductive process, a process which left unchecked threatens to swamp the world."

However, many questions and concerns have been raised by researchers, as well as by women's rights groups and health activists who question the reliability and safety of immunological contraceptives and are worried about their potential to be used coercively.

Will the manipulation of the immune system into attacking body substances ever be safe and reversible? Will women become fertile again whenever they want to? Will there be health risks for women or their future children? Will the design of these contraceptives make abuse and

coercion possible? Are clinical trials being carried out with proper precautions and care? Will these contraceptives prevent the transmission of STDs and AIDS? Why are they being especially promoted for use in Third World countries?

This publication discusses some of these questions with the aim to raise a public debate. This is a unique opportunity to take part in a scientific and socio-political discussion about a new contraceptive while it is still being developed, drawing from experiences with long-acting contraceptives, such as hormonal implants or injectables. There is often a trade off between safety and user control on the one hand, and gains in efficacy on the other hand. In coercive environments, contraceptives can be used in a way which suppresses and violates women's reproductive rights and interfere with their physical well-being. Contraceptive abuse has not only been directed against Third World women, but also against minority groups in industrialised countries. These experiences and the explicit population control objectives guiding the funding for research set the framework within which the efficacy, safety, reliability, and potential for abuse of immunological contraceptives should be evaluated.

Why are immunological contraceptives being especially promoted for use in Third World countries?

In 1989, the author of this report attended a symposium held by WHO's Human Reproduction Programme (HRP) as a consumer representative. This symposium discussed various aspects of immunological contraceptives, such as medical, social, political and legal aspects. She was invited by the HRP to participate in another meeting, to which representatives of women's and women's health groups were invited in August 1992. Her experiences with these two meetings as well as many discussions with scientists from different disciplines are the basis for this analysis. This report was written because very little information on immunological contraceptives is available to the interested public, yet a public debate urgently needs to be initiated before immunological contraceptives reach the market and become a "fact of life".

It is very urgent to initiate a public debate before immunological contraceptives become a "fact of life"

The publication is organised as follows:

The first chapter briefly introduces the immune system and the mode of action of immunological contraceptives, and presents an overview of current research. The second chapter describes the various immunological contraceptives that are currently being researched in greater detail.

The main part of the publication is a risk/benefit assessment of immunological contraceptives, focusing primarily on anti-hCG-contraceptives, which are at the most advanced stage of development. First, efficacy, reversibility, and safety are examined because these are minimum requirements for a new contraceptive. The potential for abuse is discussed as this is an important aspect of the design of a contraceptives, and the benefits that have been attributed to immunological contraceptives are analyzed. This forms the basis for a discussion of clinical trials, including ethical questions about the trials. Trials in human subjects are justified only if the new drug or contraceptive offers an advantage over existing methods, as the Declaration of Helsinki of the World Medical Association states in its introduction (CIOMS & WHO 1993).

Pregnancy is no epidemic

Throughout this publication, we call the new contraceptives *immunological contraceptives* and try to avoid the term *vaccines*. There are several reasons for this. First, immunological contraceptives should not be confused with vaccines against diseases since they rely on auto-immunisation — against body substances — as opposed to immunisation against disease. Secondly, pregnancy is neither a disease nor an epidemic. It is a natural and healthy process based on an individual couple's or woman's decision to have a child. Thirdly, the fetus is neither a germ nor a microbe invading the body and threatening it with sickness nor endangering its life. Preventing pregnancies is not like fighting a disease, and contraceptives are meant for use by healthy women and men.

A New Method for Fertility Control: Immunological Contraceptives

"...we are dealing with two of the most complex parts of the body, the immune system and the endocrine system." (Mitchison 1991)

Immunological contraceptives use the body's immune system to prevent pregnancy. Not only is this a new approach to controlling fertility; immunological contraceptives also differ fundamentally from conventional vaccines. This chapter briefly describes how immune responses may be used to interfere with reproduction and the different types of immunological contraceptives currently being developed.

The immune system: a juggling act between defence and self-tolerance

The immune system is known as the 'police of the body', providing a defence against invasion by infectious micro-organisms such as viruses, bacteria, parasites and fungi. Its efficacy is based primarily on two features:

- the ability to respond specifically to each type of micro-organism;
- memory, so that once a person has developed an immune response against a specific germ, a similar response will occur every time they are exposed to the germ.

When micro-organisms invade a person's body, they provoke an immune response when the immune system recognises them as foreign and tries to eliminate them. The first immune response against a specific micro-organism, called a *primary immune response*, is relatively slow and inefficient. A person usually becomes ill and then gets better as the immune response takes hold. However, this primary response triggers antibody producing cells to produce antibodies which are specific to the invading micro-organism, as well as other cellular processes. Thus, subsequent infections with the same micro-organism will elicit a *secondary immune response*, which is a much faster and more vigorous defence. A secondary immune response usually either prevents the outbreak of disease or greatly reduces its severity. A specific type of white blood cells, the lymphocytes, are responsible for the immune reactions.

Because of this process of immunological memory, an immune response is rarely reversible once it has been induced. However, it may dwindle to a low-level response over time. This is why certain types of vaccines, such as tetanus, require booster shots. Antibodies are transported to all parts of the body through the circulation of blood and lymph.

The immune system must distinguish between foreign micro-organisms and body components in order to work properly and to attack only foreign substances. This protection of a person's own body constituents against attack by the immune system is known as *self-tolerance*. How the immune system learns to differentiate between "self" and "non-self" is not well understood. This learning process starts during fetal development. Auto-immune diseases may occur if self-tolerance fails to work properly. These include conditions such as rheumatoid arthritis, diabetes, and myasthenia

gravies. Although symptomatic treatment exists for some auto-immune diseases, none can yet be cured.

Reproduction represents a special challenge to self-tolerance

Reproduction represents a special challenge to self-tolerance since many cellular components and hormones appear for the first time at puberty. The immune system does not attack them although they are new substances in the body. For example, sperm are protected from blood circulation by a tight barrier within the testicle and thus do not encounter any white blood cells. Anything interfering with this blood/testis barrier can cause an auto-immune reaction which may result in infertility. In women, the maturation of the egg is similarly protected. Sperm have little contact with white blood cells and other components of a woman's immune system as they travel through her uterus and fallopian tubes to fertilise the egg. This protects them from being attacked as foreign invaders. In rare instances these self protecting mechanisms are disturbed and antibodies against sperm may be found.

The fertilised egg which implants itself into the uterus is genetically different from the woman and thus might be prone to attack by her immune system. However, many processes prevent this attack, including the barrier against contact with the woman's immune system formed first by the trophoblast and later by the placenta. The fetus' developing immune system also treats maternal cells as self-like.

This delicate interaction of processes which protect early pregnancy can be disturbed. Scientists now think that immune factors play a role in a high proportion of miscarriages in early pregnancy. Some forms of infertility are also known to be caused by immunological responses to reproductive processes. For example, a man may develop an immune response to his own sperm or a woman may develop an immune response to her sexual partner's sperm, preventing conception (Pavia et al. 1987:625).

These instances of disturbed self-protection suggested the idea of developing contraceptive methods which are based on an immune response.

Immunological contraceptives

Immunological contraceptives induce an auto-immune response

Immunological contraceptives work by interfering with self-tolerance and inducing an auto-immune response, an attack against body constituents or hormones which are usually tolerated and which are necessary for reproduction.

To achieve this, researchers have had to look for appropriate reproductive target substances and to trigger the immune system to attack them. Body components do not usually provoke an immune response. To provoke this response, researchers have to make the body component appear foreign and thus combine part of the reproductive substance to a carrier, for example an altered tetanus toxoids. The combined molecule then provokes an immune reaction not only against itself, but also against its natural counterpart in the body. This attack may prevent conception or pregnancy from occurring.

Any foreign substance which enters the body and provokes an immune response is called an antigen. Since the aim is to make a reproductive substance which is usually protected by self-tolerance antigenic, researchers talk of this substance as a target antigen.

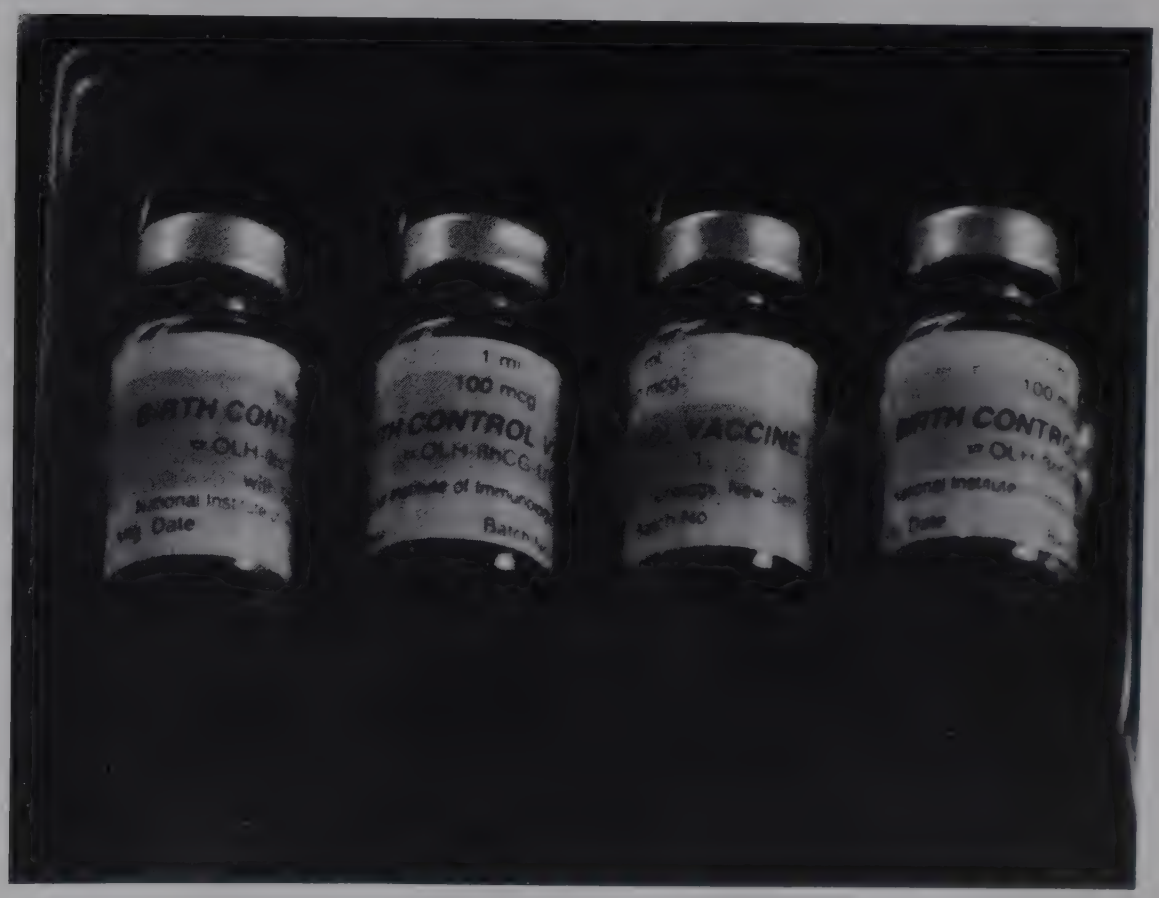
Currently, research is being carried out on a number of potential antigens. Some of these are being developed as contraceptives to be used by women; others are for men. Their mode of action is similar but their effects differ considerably depending on what antigen has been chosen.

Immune contraceptives interfere with the following processes:

- maturation of eggs and production of sperm
- fertilisation
- implantation and development of the early embryo.

Maturation of eggs and production of sperm

To disturb the maturation of egg cells or the production of sperm, the hormones GnRH (gonadotrophin releasing hormone), FSH (follicle stimulating hormone) or LH (luteinising hormone) must be attacked. All of these hormones are present in both women and men. They are *non-pregnancy associated hormones*, reproductive hormones which are present all of the time, not just during pregnancy.



The menstrual cycle is controlled by a complex feedback between several hormones

GnRH is secreted by the hypothalamus in the brain and causes the pituitary gland to secrete FSH and LH. FSH and LH in turn affect a woman's ovaries, causing the production of oestrogen and progesterone and the maturation and release of the egg during each menstrual cycle. The

menstrual cycle is controlled by a complex feedback between the hormones released by the ovary, the pituitary gland and the brain. In men, FSH and LH cause the testes to produce testosterone and sperm.

Research is being done on immunological contraceptives which act against GnRH and FSH. In women, these contraceptives would prevent both egg maturation and the hormonal changes which occur during a normal menstrual cycle. In men, they interfere with the production of testosterone and sperm.

Fertilisation

One way to prevent fertilisation of the egg by a sperm is to render either cell non-functional. Researchers are trying to find structures on the surface of the egg and sperm cells against which an auto-immune attack could be directed.

Implantation and development of the early embryo

hCG is essential for maintenance of pregnancy

Currently the most advanced research is on methods which attack the hormone hCG (human chorionic gonadotrophin). HCG is essential for implantation of the early embryo and therefore for pregnancy. It is secreted by the early embryo and instructs the woman's ovary to keep on producing progesterone. Without hCG, progesterone levels drop and the lining of the uterus cannot be maintained in the thickened state which is needed for implantation of the embryo. The lining of the uterus is shed and a woman has a menstrual-like period.

The trophoblast, a part of the early embryo which later forms the placenta, is another target antigen. Immunological contraceptives directed against the trophoblast attempt to cause the fertilised egg cell to be coated by antibodies and prevent it from implanting in the woman's uterus.

A number of different immunological contraceptives are at present being investigated. Their efficacy and risk profiles differ from each other, but they all work by inducing an immune response against a reproductive constituent which is normally protected through self-tolerance. It is unclear at present whether one, some, or all of the immunological contraceptives being studied will eventually be marketed. Some types are still at a very early, exploratory stage of research. By late 1992, only anti-hCG, anti-GnRH and anti-FSH contraceptives have reached the stage of being tested in humans. Research on anti-hCG contraceptives is by far the most advanced. This report focuses mainly on anti-hCG contraceptives as this now appears to be the most likely type of immunological contraceptive to reach the market.

Figure 1
Steps in Contraceptive Research

Step 1: Chemicals which look promising are tested in the laboratory, or in the case of immunological contraceptives, target antigens and additional agents (carriers and adjuvants) which look promising are isolated. This step can take up to 10 years.

Step 2: Animal tests of chosen substances are carried out if the results of laboratory tests are positive, to find out how a product works and what effects it has. These animal studies take one to two years.

Step 3: Phase 1 clinical trials are carried out in 10-20 previously sterilised volunteers. These studies test for toxic effects, dosage and pharmacology, not for effectiveness as a contraceptive. Phase one trials last one to two years.

Step 4: More animal testing is done to look at safety if the early human trials did not find toxic effects. These trials look for effects on reproduction and risks of birth defects, genetic changes (mutations) and cancer. They are carried out in various types of animals, including rodents and primates.

Step 5: Phase 2 clinical trials are carried out on up to a few hundred fertile volunteers during a six month to two year period. Phase two trials differ from phase one in that effectiveness is tested as well as safety and pharmacology.

Step 6: Phase 3 trials are carried out. These trials involve from several hundred to over a thousand people and can last one year or longer. They are generally carried out in various countries. Both phase two and phase three trials test for effectiveness, dosage and side effects.

Step 7: Acceptability studies. This is a new part of the development process, which studies the use of a method within family planning programmes and how acceptable users find it. The most common measure of acceptability is the percentage of contraceptive users choosing to continue or discontinue use.

Step 8: National drug regulatory authorities approve and register the contraceptive after receiving information on laboratory, animal and human studies from the manufacturer.

Step 9: Distribution and marketing

Step 10: Post-marketing surveillance is carried out to discover rare or long-term effects.

(Hardon 1992; HRP 1988)

AN OVERVIEW OF CURRENT RESEARCH

Five major and four smaller teams operating on four continents are carrying out research on immunological contraceptives.[1]

HRP

World Health Organization (WHO): HRP

WHO has a Special Programme of Research, Development and Research Training in Human Reproduction (HRP) which includes a Task Force on Vaccines for Fertility Regulation.

Coordinator: David Griffin, Task Force Manager

Focus of research: anti-hCG contraceptive. Phase 1 clinical trials in Australia completed; Phase 2 clinical trials will start in Sweden in 1993.

Main researchers: Vernon Stevens, Ohio State University, Columbus, USA. Warren R. Jones, Flinders Medical Centre, Adelaide, Australia.

Funders (for the HRP as such): United Nations Development Programme (UNDP); United Nations Population Fund (UNFPA); World Bank; governments of Denmark, Norway, Sweden, United Kingdom, Federal Republic of Germany.

NII

National Institute of Immunology (NII), New Delhi, India

Coordinator: G. Pran Talwar, Professor of Eminence and former Director of the Institute

Focus of research: nearly all types of immununological contraceptives. Phase 1 clinical trials with an anti-hCG-oLH-formula have been completed and Phase 2 clinical trials are currently being evaluated. Clinical trials with anti-GnRH-formulas in men with prostate cancer and in post-partum women. Research on anti-FSH-contraceptives.

Main researchers: Pran Talwar and colleagues.

Funders: Indian government; International Development Research Centre (IDRC), Canada; Rockefeller Foundation, USA; CONRAD?

Population Council

Population Council, New York:

Coordinator: Rosemary Thau, Director of Contraceptive Research

Focus: anti-hCG, anti-GnRH contraceptives (as yet only in cancer patients); also research on anti-FSH contraceptives for men and identification of anti-sperm immunological contraceptives for women.

Main trial centres (for anti-hCG-contraceptives): Helsinki, Finland; Santo Domingo, Dominican Republic; Santiago, Chile; earlier trials were also held in Uppsala, Sweden and Bahia, Brazil.

Funders: Andrew W. Mellon Foundation; Georg J. Hecht Fund; Dodge Foundation; Rockefeller Foundation; National Institutes of Health; USAID[2] - all USA.

CONRAD

Contraceptive Research and Development Programme (CONRAD) at the Eastern Virginia Medical School, in Norfolk, Virginia, USA

Coordinator: Henry Gabelnick, Program Director

Focus of research: CONRAD intramural projects at the Eastern Virginia Medical School are currently limited to pre-fertilisation methods, and are concentrating on identification of sperm antigens and antigens of the zona pellucida. Clinical trials with anti-sperm contraceptives may start in 1994/95 (Browne 1991). CONRAD also channels USAID funds into numerous extramural projects.

Main researchers: John Herr, Eastern Virginia Medical School. Paul Primakoff, University of Connecticut, Farmington, USA (anti-sperm contraceptives). Research teams of the bilateral Contraceptive Development and Research in Immunology (CD&RI) collaborative projects which are co-funded by CONRAD and the Indian Government.

Funders: USAID[2]

NICHD

National Institute for Child Health and Development / National Institute of Health (NICHD/NIH), Bethesda, Maryland, USA.

Coordinator: Gabriel Bialy, Chief of the Contraceptive Development Branch

Focus of research: anti-sperm and anti-egg contraceptives.

Funders: US government[2]

Other research teams

Independently of the major teams, a number of smaller research teams are also working on immunological contraceptives. They include:

- John Aitken of the Reproductive Biology Unit of Edinburgh University (UK) and Jacques Testard of INSERM (Institut National de la Santé et de la Recherche Médicale, France). Focus: anti-egg contraceptives.
- Peter M. Johnson of the Department of Immunology, University of Liverpool (UK). Focus: anti-trophoblast contraceptives.
- Dominique Bellet of the Institut Gustave-Roussy (France). Focus: anti-hCG method.
- M.R. Moudgal from the Indian Institute of Science, Bangalore, India. Focus: anti-FSH contraceptives for men.

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1 This overview may be incomplete as data on trials and funding are not easily accessible. Only main funders are listed. With the exception of the HRP, which receives funding for its entire programme, funds are usually bound to *specific* research projects.

2 Currently, funding from the United States government is only available for pre-fertilisation methods. This affects the research priorities of the Population Council, CONRAD and NICHD/NIH. This situation has not changed yet (mid-1993) but it may change soon as it is related to anti-abortion policies brought in during the Reagan and Bush administrations.

CHARACTERISTICS OF IMMUNOLOGICAL CONTRACEPTIVES

"No method of regulating fertility has ever before rested on immunological principles, nor has any vaccine ever been directed towards the inhibition of a 'self-like' component or secretion" (Spieler 1987)

Immunological contraceptives are often compared with anti-disease vaccines in both the scientific literature and the press. For example, Sheldon Segal states that "Immunisation against diseases has proven to be the most effective approach available for disease prevention. It may also become a technology for pregnancy prevention." (Segal 1991:9) David Griffin speaks about, "the objective being to use the body's own immune system to provide protection against pregnancy in essentially the same way that it provides protection against unwanted diseases." (Griffin 1992:3) These comparisons obscure fundamental differences in the mode of action of immunological contraceptives, as compared to anti-disease vaccines.

This chapter describes both the similarities and differences between immunological contraceptives and vaccines. Because of these differences, the development of immune contraceptives poses specific problems not encountered during vaccine development.

Principle of action

Immunological contraceptives are similar to vaccines in so far as their effects are mediated by the immune system. In contrast to 'pharmacological' medicines or contraceptives "their active principle is not what is injected but what is produced by the body in response." (Talwar et al. 1990:585). There is one crucial and profound difference, however: anti-disease vaccines act through *immunisation*, i.e. through induction of the specific immune defence against *foreign* micro-organisms, whereas anti-fertility 'vaccines' act through *auto-immunisation*, i.e. the induction of abnormal immune responses against *self* or *self-like* body components or secretions which are essential for human reproduction.

Effects

The desired effect of anti-disease vaccination is the prevention of harmful or life-threatening diseases. The purpose of anti-fertility auto-immunisation is to provide reliable and reversible contraception.

Vaccines are effective not only on an individual level but also through mass immunity. If an immune response is induced in the majority of a vaccinated population, everyone gains from it. Even if one person's immune system has not reacted strongly to the vaccine, that person is protected if most people around them are protected because they are less likely to be exposed to the disease. Similarly, the duration of action does not need to be exact. The longer the immunological memory, the better, because the ultimate goal is lifetime protection against a disease.

However, for anti-fertility 'vaccines' the aim is to induce an immune response which is reliable in each individual and occurs for a limited period of time. This is a complete novelty. As Griffin states "Unlike anti-disease vaccines, anti-fertility vaccines are not intended to provide lifetime immunity but rather to produce an effective immune response of predictable and comparatively short duration." (1990b:508) Because

pregnancy is not an infectious disease, broad coverage in a population provides no protection for an individual woman. Similarly, "the longer the better" principle of vaccines does not apply to contraceptives, which people use because they want to avoid pregnancy over a specific, known period of time.

Undesired effects

For anti-disease vaccines, these include the outbreak of the disease in the immunised person or immunological adverse effects such as allergies. Undesired biological effects of anti-fertility auto-immunisation include life-long sterility, immunological adverse effects and damage to future offspring.

Will it be possible to induce a time-limited auto-immune reaction?

Research on anti-fertility auto-immunisation methods thus faces two fundamental challenges: Will it be possible to induce a predictable, time-limited auto-immune reaction? Can this be done without inducing unacceptable adverse effects? These questions cannot yet be answered, but given the research findings so far, and our present knowledge about the immune system, there are reasons to doubt that it will be possible.

What is needed for an immunological contraceptive?

Currently, immunological contraceptives consist of three main parts:

- the antigen made of the reproductive substance;
- a formulation which increases the potency of the response. The antigen is usually bound to a carrier molecule. One or more adjuvants are added to strengthen the immune response. The oily emulsion used as a delivery system can further enhance this response.
- a specific schedule for immunisations.

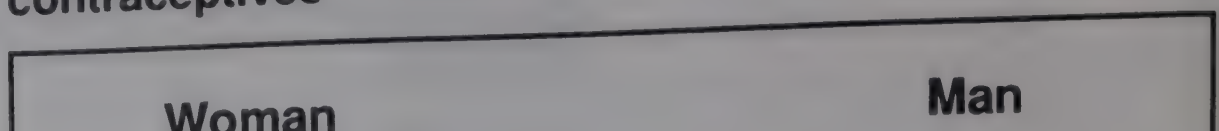
Antigens

As briefly outlined in chapter one, a molecular structure must be found that can be made antigenic and thus elicits an immune response against itself and its natural counterpart when reintroduced into the body. The challenge lies in selecting an antigen which is at the same time *essential* and *specific* or unique to reproduction. The antigen is considered essential if an attack of its natural counterpart will lead to an interruption of the reproductive process which can prevent pregnancy. It should be specific, in other words different enough from other structures in the body, to avoid also provoking an immune response against them. The target antigen should only have a *single* function in the body related to reproduction. If it has several functions, these will also be interrupted. Finding such an antigen has proven very difficult.

It has proven very difficult to find an appropriate target antigen

If the whole molecule of a hormone or a whole cell is used as an antigen, it will provoke the production of many different antibodies because it consists of several different antigenic determinants. As some of these are similar to other hormones or other structures in the body, they will provoke an immune response against these other structures. This is called a *cross reaction*. To make the candidate antigen more specific, researchers try to use only part of the molecule. However, a small part of the molecule

Figure 2
Possible target substances for immunological contraceptives



modified from Ada & Griffin 1991c

Possible target sites for immunological contraceptives are printed in *italics*. The figure also shows the interplay of hormones during reproduction.
⇩⇧ means: "acts on".
➧ means: "leads to".
The hypothalamus is a region of the brain and the pituitary is a gland within the brain. For explanation of hormones see glossary.

The immune system must be tricked into treating a body component as foreign

cannot elicit an immune response on its own. To work effectively, it is attached to a carrier. Diphtheria, tetanus and cholera toxoids[1] have been used as carriers. The use of a carrier has two advantages. First, the resulting molecule looks foreign to the immune system. It is not longer protected by self-tolerance, as the hormone or structure alone would be. Second, the effectiveness of the antigen increases, because the combined molecule is bigger.

Immunopotentiators are also added to the formula. These are substances which generally enhance immune responses. Immunopotentiators include adjuvants and slow-release delivery systems such as the oily liquid in which the antigen-carrier complex and helper substances are suspended. The immunopotentiators must be tested to find out which work well and do not cause unacceptable adverse effects.

An immunisation schedule consists of a primary immunisation schedule, which is the number of injections required to reach an effective level of protection against contraception, and the schedule for refresher (booster) injections needed if a person wants to continue to use the immunological contraceptive for longer. Researchers are trying to develop an immunological contraceptive which would act after one or at most two injections, with booster injections every one to two years (Basten et al. 1991:92).

Figure 2 gives an overview of the potential target substances used to design an immunological contraceptive. They are discussed in detail below.

The most advanced candidate: anti-hCG immunological contraceptives

For many researchers, the most promising target antigen is the pregnancy associated hormone hCG (human chorionic gonadotropin). This hormone is secreted by the early embryo shortly after fertilisation. It acts on the corpus luteum, a glandular structure on the surface of the ovary which is formed after the egg leaves the ovary at ovulation. The hormone hCG stimulates the corpus luteum to continue producing progesterone. Progesterone is essential to prepare the womb for implantation and maintenance of early pregnancy. If hCG is intercepted by anti-hCG antibodies, the corpus luteum shrivels, the progesterone level drops and the early ovum is expelled with the menstruation.

hCG seemed to be the perfect antigen

When the researchers began, they believed that "the advantage of immunising against... human chorionic gonadotrophin (hCG) is that the antigen is probably present in immunised women only at times of incipient pregnancy, and that risks of side-effects would therefore considerably be minimised." (Task Force 1978:368) The hormone hCG seemed to be the perfect antigen, since it would need to be neutralised at most once per month, i.e. whenever an egg was fertilised. Furthermore, it seemed to have no other function in the woman's body. WHO's HRP, the Population Council and the Indian NII all began research on anti-hCG contraceptives.

Yet, hCG poses a specific problem. It structurally resembles to the reproductive hormones LH, FSH and TSH (thyroid-stimulating hormone). If the complete hCG molecule is used as an antigen, it leads to immunological cross reaction in that antibodies against hCG also attack the other hormones. This could interfere with the menstrual cycle and thyroid functioning and could damage to the pituitary and the thyroid glands.

To resolve the problem of cross reactions, scientists decided to break down the molecule and look for a more specific antigenic determinant.

Cross reactions can damage other body functions

HCG and the related hormones FSH, LH and TSH are composed of two subunits: a short alpha-subunit and a longer beta-subunit. While the alpha-subunit is virtually identical for all four hormones, the beta-subunit of hCG is similar only to that in LH. The hCG beta-subunit has a small section at its end which is not found anywhere else. The HRP research team opted for this small piece as their candidate antigen whereas Talwar from NII and the Population Council chose the complete beta-subunit, hoping that cross reactions with LH would not cause adverse effects (Brache et al. 1992:10).

HRP's anti-hCG contraceptive

HRP developed a genetically engineered candidate-antigen which is known as "beta-hCG-CTP vaccine" or "beta-hCG peptide vaccine" from the last 37 amino acid sequence[2] of the beta subunit (= carboxyterminal peptide, in short CTP). It is attached to a diphtheria toxoid and mixed with an adjuvant and delivered in an oily emulsion. Although this anti-beta-CTP-hCG formula does not appear to induce cross reactions with LH (Stevens 1986), its has caused cross reactions with cells in the pituitary gland and in the pancreas (Rose et al. 1988:231-239). Moreover, the assumption that hCG would be produced only by the early embryo and thus be specific for this phase of pregnancy was shaken by the finding that it may be "released in non pregnant women, presumably from the pituitary, in small amounts which vary with the menstrual cycle." (Mitchison 1990:725) The role of this non-pregnancy-associated hCG is unknown and might, according to Griffin (pers comm) only be a false reading resulting from small inaccuracies in laboratory tests (artefact). However, if these findings are correct and if hCG has a function in the body at other times, it would no longer have the advantage of specificity to pregnancy.

The other anti-hCG contraceptive

The Population Council and NII have followed a different approach. In their opinion, HRP's antigen will never produce an efficient enough immune response to be a good contraceptive. They have deliberately chosen to use the whole beta-subunit, a fragment which is not specific to hCG. As expected, their anti-beta-hCG formula leads to cross reactions with LH. However, both teams claim that the cross-reactive auto-immunity did not result in expected adverse effects such as menstrual disturbances. Rose et al questioned this lack of biological effect at the meeting on immunological contraceptives sponsored by HRP: "Why isn't the bioactivity of hLH (human LH) impaired or even completely abolished in these subjects, when their immune responses are considered adequate to neutralise hCG?" (1991:131)

Animal studies to resolve the question of long-term adverse effects should be a high priority

It is far too early to make claims about safety because potential severe long-term effects, such as damage to the ovaries or pituitary gland, might occur only after years of repeated auto-immunisation. HRP emphasised that "resolving the issue [of long-term adverse effects] in appropriately designed studies in relevant animal models should be a high priority in future research with this vaccine." (Griffin 1992:8)

The hope that the whole beta-subunit would trigger a satisfactory anti-fertility effect has not yet been achieved. The efficacy of both the Population Council and the Indian anti-hCG preparations are far from ideal. In the first clinical trial, the immune response of one quarter of the women did not reach the theoretically necessary threshold (Jayaraman 1986:661). Talwar of the Indian NII therefore decided to change the antigen. He combined beta-hCG with the alpha-subunit of LH from sheep (ovine LH, in short oLH). His rationale was that the antigen would thus resemble the whole hCG molecule more closely without leading to additional cross reactions with human LH. This has turned out to be untrue; cross reactions have occurred.

The US Food and Drug Administration (FDA) refused Talwar's application for approval of his clinical trials with this combined antigen because of the increased risk of cross reactions (Thau 1992). The Indian Drug Control Authority, however, did approve of the clinical trials. Talwar sees no problem in the increased risks of cross reactions; he declares that cross reactions with LH are desirable because neutralisation of LH will contribute to the effectiveness of the contraceptive (Brache et al. 1992:10).

Unsatisfactory efficacy remains a major problem

Apart from the unknown consequences of cross reactions, unsatisfactory efficacy remains a major problem for all of the anti-hCG contraceptives. HRP's current formulation, for example, would require booster injections every two to three months (Stevens 1990:563). The Indian formula

requires a booster every six to eight months (Talwar et al. 1992a:5) and the Population Council's formula is as yet unsatisfactory (Thau et al 1990:243). They are hoping that a change in formulation will increase the effectiveness of their contraceptives. The HRP team and the Indian researchers plan to incorporate their hCG-carrier conjugate into tiny biodegradable particles (microspheres) in which the antigen is enclosed. These microspheres cause the formula to be slowly released into the body. Whether or not the new formulations will achieve a satisfactory efficacy profile is still unknown.

Using other hormones as antigens

Several teams are exploring the use of GnRH and FSH, non-pregnancy associated hormones, as antigens. These hormones control a number of functions related to sex and reproduction, such as the maturation of eggs and production of sperm, control of the menstrual cycle, secondary sex characteristics and libido.

Hormones interact through a complex regulatory system

GnRH and FSH act within regulatory feed-back loops. Their presence in the bloodstream determines whether the pituitary releases the hormone LH, whether women's ovaries release oestrogen and progesterone, and whether men's testes release testosterone. The presence of these hormones in the blood in turn controls the release of GnRH by the brain and the release of FSH by the pituitary. Disturbance of these regulatory mechanisms are likely to cause adverse effects.

Furthermore, the desired auto-immune reactions may attack the hormones at three stages: during hormone synthesis, during their circulation in the blood, and at their target cells. Two major problems could arise:

- If GnRH and FSH are intercepted during circulation in the blood, this may interfere with all the biological effects of the hormone, not only with sperm or egg maturation. According to Chard and Howell, potentially a "very wide range of disorders" could be caused by the hormonal imbalances induced (1991:97). Some, such as organ damage caused by the atrophy of an organ without hormonal stimulation, might emerge only after long-term neutralisation.
- GnRH and FSH may become bound by antibodies when they are being secreted or when they are attaching to their target cells. Since they are then in contact with a cell, the antibody attack might lead to cell destruction. This is known as a cytotoxic — cell killing — effect. Cytotoxic effects "might represent some of the most significant risks of immunisation to self-antigens." (Chard & Howell 1991:99). Organ damage can also occur if significant numbers of cells are killed because of these cytotoxic effects.

Auto-immunisation against GnRH and FSH interferes with the hormonal system

In short, auto-immunisation against GnRH or FSH may interfere with a complex hormonal regulatory system. "The unknown consequences of chronic [i.e. long-term] immunity to 'self' molecules in the brain, pituitary gland and gonads would argue against using immunogens restricted to these sites", was the conclusion of the experts at the 1989 HRP Symposium (Report... 1991:255). HRP has decided not to develop contraceptives based on these antigens because of their concerns about these risks (Ada & Griffin 1991b:9).

However, in late 1992 the Population Council and NII were both conducting human clinical trials with anti-GnRH preparations in men. The current anti-GnRH trials are testing the effects of auto-immunisation on cancer of the prostate.[3] However, the researchers have stated that their ultimate aim is to develop an anti-GnRH contraceptive (Thau 1992). The US. Food and Drug Administration has not yet allowed this method to be tested in healthy men.

NII is also conducting trials on women — just after giving birth — using auto-immunisation against GnRH to prolong lactational amenorrhea in postpartum women (Talwar 1990:723). These trials raise concerns about the effects on infants of exposure in breast milk to a contraceptive which induces an auto-immune response, as well as concerns about the ethics of including breast feeding women in a trial of a new contraceptive.

Another Indian researcher, N.R. Moudgal, is testing anti-FSH contraceptives in men (Talwar 1992)

Using parts of eggs or sperm as antigens

The development of safe anti-sperm or anti-egg immunological contraceptives poses different problems. The desired auto-immune response has to damage the mature egg or sperm cells in a way that prevents fertilisation without damaging other tissues.

It sounds elegant and safe to induce an auto-immune reaction against just one tiny body component once a month

It sounds elegant and safe to induce an auto-immune reaction against just one tiny body component once a month — namely the one egg which ripens for fertilisation. However, researchers have found it very difficult to identify structures on the surface of the mature egg which are not also present on immature eggs within the ovaries. Otherwise, an auto-immune response could eradicate all of a woman's eggs and make her infertile as well as damaging the surrounding ovarian tissues and preventing the production of oestrogen and progesterone by the ovary.

Current research focuses on different surface antigens on the zona pellucida (ZP), a translucent membrane which surrounds the egg only in late stages of maturation. However, animal trials of these immunological contraceptives have caused ovarian abnormalities (Ada & Griffin 1991c:21).

Anti-sperm auto-immunisation also faces the problem that immune reactions which affect sperm in the testis can cause a chronic auto-immune inflammation of the testis (orchitis) which ultimately leads to infertility. Researchers are therefore searching for cell-associated antigens that are expressed only after the sperm have left the testis (post-testicular antigens).

To avoid adverse effects in men, researchers are now developing anti-sperm contraceptives for women

Women who feel relieved that an anti-sperm method will free them from the burden of contraceptive side effects will have to reconsider. Researchers have tried to avoid the problems of testicular inflammation by developing an anti-sperm contraceptive for women. Here also, many problems remain to be solved. First, sperm are usually not affected by a woman's immune system because they stay within the reproductive tract and are not exposed to the body's circulatory systems. To attack them, the

immune system must be manipulated in a complicated way to produce a type of antibodies which are secreted and are therefore present within a woman's reproductive tract. Secondly, there is a large amount of sperm to be neutralised each time a couple has intercourse. Many sperm are present even in the upper part of the uterus and the Fallopian tubes. Thirdly, the desired auto-immune reaction must be efficient, reliable and fast no matter how frequently a couple has intercourse, since a single sperm cell can fertilise an egg within a few hours.

A last problem with cell-associated antigens, as for the hormones, is that they could show unforeseeable similarities with other molecular structures in the body. This could lead to unexpected cross reactions following anti-egg or anti-sperm auto-immunisation. For example, some sperm antibodies were found to cross react with brain and kidney tissue, lymphocytes and red blood cells (Naz 1988, quoted in Schrater 1992).

Developing a safe and efficient anti-egg or anti-sperm immune contraceptive has proven much more difficult than anticipated

Developing a safe and efficient anti-egg or anti-sperm immune contraceptive has proved much more difficult than the researchers anticipated, given the unusual and complex tasks which they are demanding from the immune system. Although many potential cell-associated antigens have been screened for suitability, development of anti-egg and anti-sperm contraceptives is the least advanced of all the research (Griffin 1992:9). Human testing had to be postponed repeatedly. Jeff Spieler, for example, believed in 1987, that "vaccines interfering with sperm function and fertilisation could be available for human testing by the early 1990s." (1987:779) John Herr of the University of Virginia at Charlottesville hopes to be able to ask for permission for human trials by 1995 (Browne 1991).

Auto-immunisation: the underlying problem

The problem of finding the right target structure to interrupt a reproductive process should not be underrated. Depending on the role, location, and structure of the target antigen, different problems have occurred and will continue to arise when the prototype formulas are tested in animal and clinical trials. The researchers assert that they will solve these problems by identifying new antigens or improving the formulation. However, the basic principle of immunological contraceptives remains: the induction of an immune attack against a body substance which is usually protected by self-tolerance mechanisms. Some researchers doubt that it will ever be possible to induce a satisfactory anti-fertility effect without inducing unacceptable adverse effects. David Hamilton from the University of Minnesota confronted his fellow researchers at the end of the 1989 CONRAD Symposium:

"We have heard during the meeting that zona pellucida antigens cause atrophy of the ovary ... And in the male, even immunisation with very sperm-specific surface antigens cause orchitis. Yet now it has been suggested ... to get [still] more specific antigens. But doesn't the inherent problem remain — that we are immunising against body constituents and that this may cause auto-immunity? Although you may say we have examples already from human chorionic gonadotrophin (hCG) immunisation, I think that these cases have not been followed properly.

"I am very sceptical that immunisation against body constituents would ever work without side-effects"

What do we know about those women who were immunised? Do you know what sort of delayed auto-immune disease is possible? I am very sceptical that immunisation against body constituents would ever work without side-effects." (in Alexander et al. 1990:615)

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1 Toxoids are an altered form of toxins secreted by micro-organisms. They have been altered to avoid the health risks of the original toxin.

2 Amino acids are basic elements of proteins. A short sequence of amino acids is called a peptide.

3 The production of testosterone, which influences tumours of the prostate, is blocked by anti-GnRH auto-immunisation.

Risk/Benefit Assessment of Immunological Contraceptives

"A feminist approach to birth control would have to take into account the present range of options women have, the context in which those choices are made and what future developments we want to see... After all we must insist that birth control, like other health care, exists for us, not we for it." (O'Sullivan 1981)

How does one judge if a new contraceptive provides a valuable addition to the range of available choices? Clearly, women and men need a range of options to meet different individual needs, cultural preferences, health requirements, and priorities based on age, parity, and availability of health services, including safe abortion facilities in case of failure. However, a variety of contraceptive methods already exists. If a new method is neither as effective nor as safe as existing methods — if it confers no real advantage — then its development is a waste of money and resources, and exposes people involved in clinical trials to unnecessary risks.

Contraceptives do not only have a function as products which prevent pregnancy, they also have a social and political function. They can enhance women's autonomy by giving greater control over childbearing, or, in the case of abuse, may remove or restrict women's choices. The design of a contraceptive can create a high or low potential for abuse. For example, the contraceptive pill and the condom have a very low potential for abuse because they are controlled by the user. Depo Provera®, on the other hand, has a high potential for abuse because of its injectable form and its effect cannot be reversed for three month.

Contraceptives can also affect women's social and sexual lives in a positive or negative way. For example, hormonal contraceptives have been praised as increasing women's sexual autonomy by freeing women from the fear of pregnancy because of their high effectiveness and independence from the act of intercourse. However, some users experience lowered libido as a side effect, which may have disturbing consequences for their sexual lives and sense of identity (Garcia & Dacach 1993:74). Contraceptives which disturb the menstrual cycle may also affect a woman's life within her community if she cannot take part in traditional ceremonies, praying and sexual intercourse while bleeding (UBINIG 1991; Hanhart 1993).

Some contraceptives provide protection against the spread of sexually transmitted diseases. This has become increasingly important with the rapid spread of AIDS. However, a contraceptive may also increase susceptibility to AIDS or other sexually transmitted diseases, or speed the onset of disease. For example, a large European study of the sexual partners of HIV-positive men found that women using an IUD had the highest risk of contracting the virus (European Study Group 1989). Injectables and implants can also increase the risk of AIDS and hepatitis B transmission if sterile equipment is not used.

This is one aspect of the quality of health services needed for safe contraceptive use. Some contraceptives are only safe within a good quality health service. For example, a contraceptive which is unsafe for certain people will be much less safe in a setting where it is difficult to exclude users with contraindications because the necessary diagnostic tests are not available.

At a minimum, a risk/benefit assessment of an immunological contraceptive needs to look at:

- ❑ effectiveness and reliability in preventing pregnancy
- ❑ risk of short and long-term adverse effects, including both
  - ❑ the possibility of rare, but serious risks,
  - ❑ the frequency of "minor" side effects like headache, menstrual disturbances etc. and their effects on well-being
- ❑ transmission of STDs and AIDS
- ❑ risks for the fetus in case of method failure
- ❑ health service requirements for safe use
- ❑ effects on social and sexual relationships
- ❑ potential for abuse.

I. EFFICACY, REVERSIBILITY, SAFETY AND PREVENTION OF STD TRANSMISSION

A contraceptive should prevent pregnancy reliably. Its effects should be reversible and neither short-term nor long-term adverse effects should pose major risks to a person's health. Because contraceptives are used by large populations of healthy people over long periods of time, safety standards need to be more stringent than for drugs to treat diseases. There should be no risk to the health of offspring after contraceptive use and as little as possible to babies born because of accidental pregnancies during contraceptive use.

This chapter looks at what is known about the efficacy, reversibility and safety of immunological contraceptives. A final section examines their potential effects on STD transmission and AIDS.

Contraceptive efficacy

No contraceptive is 100% effective. The reported effectiveness of contraceptives varies in different studies (see Table 1 on the next page). This may reflect the underlying fertility rate in the study group, which is related to age, health and frequency of intercourse, and other factors influencing the effectiveness of a particular method, such as body weight (Norplant®) or interactions with certain medicines (hormonal methods). Service provision can influence the failure rate if users are not properly informed about correct use, or if they cannot obtain a method such as the contraceptive pill or hormonal injections in time for continuous use.

Effectiveness is generally measured as the number of pregnancies per 100 women using a method for one year. *Theoretical effectiveness* rates reflect the highest possible rates expected with the use of a method, based on the results of controlled clinical trials. *Actual effectiveness* reflects failure rates in conditions of normal use, which may vary greatly.

Table 1:
Comparison of some methods of contraception

Method	Pregnancy rate per 100 women years[a]	Risk of adverse effects	Protection against STD/ HIV
Sterilisation			
Male	0-0,2	Low	No
Female	0-0,5	Medium	No
Oral hormonal contraceptives			
combined pill	0,2-7	Medium	No
progesterone only	0,3-5	Medium	No
Hormonal injectables	< 1[b]	Medium-High [e]	No[f]
Hormonal implants	0,3-1,4[c]	Medium-High [e]	No[f]
IUDs	0,3-9	High	No[h]
Diaphragm	2-20	Low	Yes/No[h]
Condom	2-20	Low	Yes
Sponge	9-27	Low	Yes/No[h]
Spermicide	4-30	Low	Yes/No[h]
Withdrawal	5-20	—	No
Rhythm	25-30	—	No
Ovulation monitoring	3-25	—	No
Breast feeding	2[d]	—	No

Source: Chetley 1993

a Large variations in pregnancy rates for some methods mostly reflect differences in how consistently or how well a method is used.

b The low pregnancy rate with injectables is dependent upon consistent use; this is more likely to occur in clinical trials than in real life situations.

c The pregnancy rate with implants is even higher in women weighing more than 70 kg.

d Breast feeding makes a substantial contribution to birth spacing and fertility control in many areas, and gives a pregnancy rate of less than two per 100 during the first six months provided the baby is nearly fully breastfed, and the mother's menstruation has not yet returned.

e Long-term safety of injectables and implants is not established; also any adverse effects may continue for the duration of the effect of the injection or until after the implant has been removed.

f Injectables and implants may increase the risk of transmission of HIV if unsterile equipment is used.

g The use of IUDs is probably a risk factor in same STDs.

h The diaphragm and some other barrier methods reduce the risk of transmission of some STDs, but have no effect in preventing the transmission of HIV.

Effectiveness of immunological contraceptives

It is not easy to assess the efficacy of an immune response. The amount of antibodies in the blood, the *antibody titre*, needs to be above a certain threshold level to show that a person has developed a sufficient immune response. However, the extent to which antibody titres can reflect true contraceptive efficacy is not completely known. For example, an antibody may have a high or low affinity for the antigen. These qualities determine how effectively the antibody binds with an antigen and therefore how strong an immune response is. However, the amount of high and of low affinity antibodies in the blood are not measured (Talwar et al 1990b:585). Also, values for effective thresholds are still theoretical. They will have to be determined in Phase 2 clinical trials, which test contraceptives on fertile humans).

Figure 3:
Effectiveness of an ideal immunological contraceptive

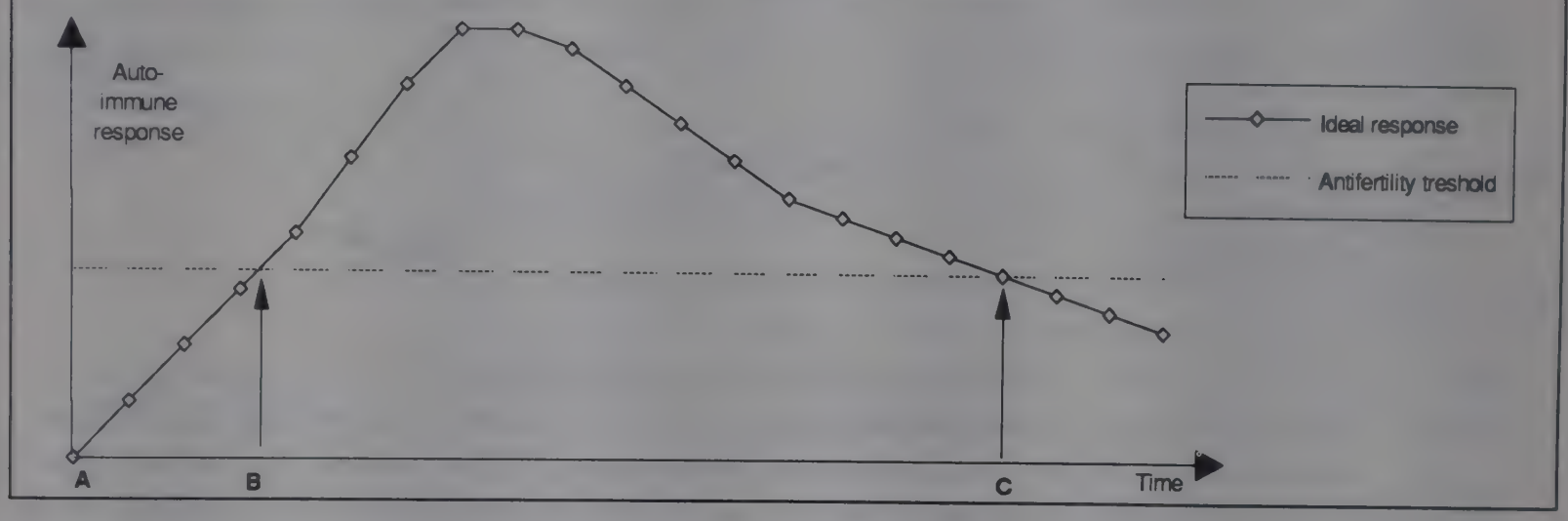


Figure 3 shows how effectiveness would ideally develop in an immunological contraceptive given as a single injection:

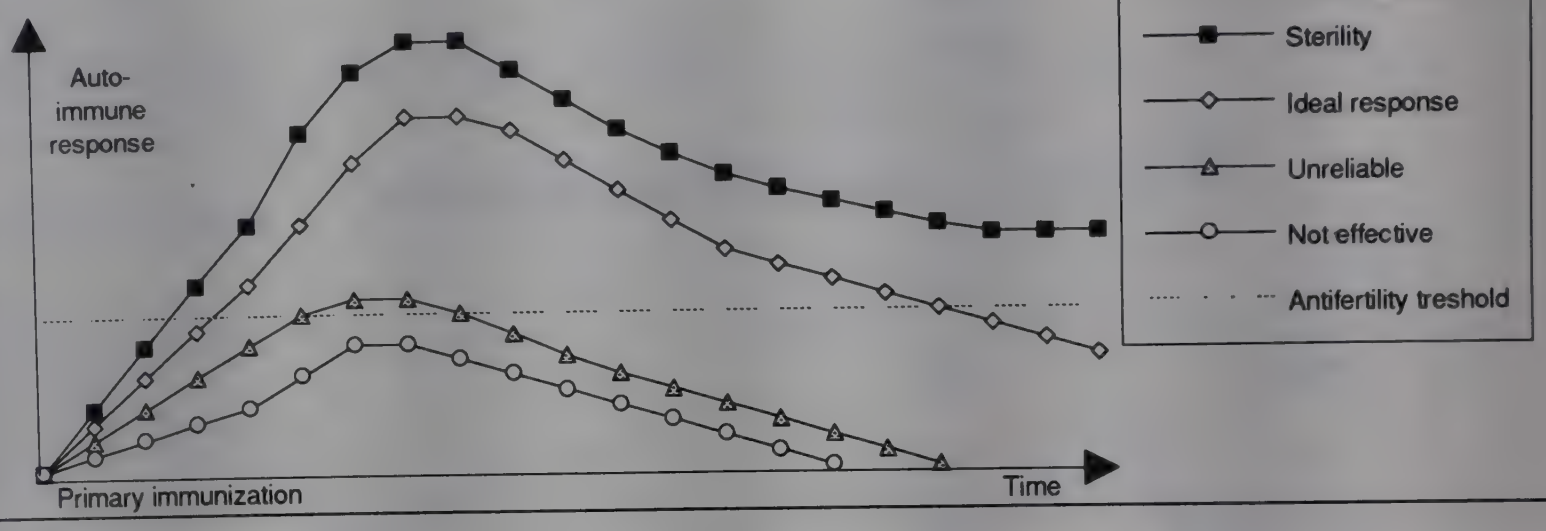
- After injection at point A, there will be first a *lag period*, i.e. the time the body needs to build up the immune response. This is true for all immune reactions. During this time, the immunological response cannot be relied upon for contraception.
- The *plateau phase*: as soon as the titre of antibodies reaches threshold (point B), protection begins and lasts until point C.
- Then the titre slowly decreases unless it drops below the effective threshold (point C). In the *waning phase* contraception is no longer reliable. Fertility returns if the contraceptive effect is not prolonged through an additional booster injection.

The reliability of an immune contraceptive thus depends on (1) the lag phase, (2) duration and magnitude of the plateau phase, and (3) the waning phase and boosting. This effectiveness profile is more complicated than for other contraceptives.

We know from vaccinations that the speed and the progress of the immune response varies between individuals. Figure 4 shows the variety of primary

immune responses that can be expected. Not all users are expected to reach the threshold within the same time. Some will not reach the threshold at all (circles). The duration of the plateau phase also differs and some people may experience no waning phase (squares). Also, a reaction is conceivable that scarcely reaches the threshold (triangle). In this case each minor disturbance of the immune system could lead to a drop in titre below the threshold.

Figure 4:
Expected variations in immune response



So far, the threshold for the antibody-titre is only hypothetical. Researchers chose a value that seemed to be realistic. Since Phase 1 clinical trials are carried out in infertile women, the concentration of antibodies needed to prevent pregnancy cannot be measured. Phase 2 trials in India on anti-hCG-contraceptives have involved fertile women, but the results do not yet clearly indicate the antibody titre threshold level needed to prevent pregnancy effectively. It still remains unclear whether a threshold — if it can be determined at all — will be valid for all women and all types of immunological contraceptives.

The lag period: exposure without effectiveness

The lag period cannot be avoided because of the nature of immune reactions. During this time, users will have received the immunological contraceptive but it will not yet have started to work.

The lag period "is not perceived as a problem that would make the vaccine unattractive"

With HRP's current anti-hCG-CTP-formula, it takes around five to six weeks to build up an antibody level that is considered protective (Jones et al. 1988). HRP's Task Force Manager David Griffin (1990:6) stated that "this [lag period] is not perceived as a problem that would make the vaccine unattractive. Synchronising vaccine administration with the menstrual cycle and/or using the monthly injectable contraceptive for the first month are two of several possible strategies that have been considered for this context."

Talwar and colleagues state that their anti-hCG immune contraceptive "takes about 3-4 months to build up antibody levels above the protective threshold. This period will be vulnerable to pregnancy and it is important to devise an approach which is compatible with the vaccine for covering this lag-period." (Talwar et al. 1992a)

Talwar's team has started to develop a method based on purified extracts of the neem tree which they inject into a woman's uterus at the same time as the first primary immunisation. They assert that this method causes a highly localised reaction over a few months and call it a VILCI-vaccine for inducing local cell-mediated immunity. They are promoting it not only as "companion vaccine" to their anti-hCG contraceptive, but also as a "vacation contraceptive"(Talwar et al. 1993:6).

An herbal extract injected into the uterus is not a vaccine in spite of the name given to it by its developers. It is a mixture of several substances extracted from the neem tree. Neem extracts have been used as pesticides and as herbal vaginal contraceptives in India. The contraceptive effect with intrauterine administration probably results from inflammation of the uterus. Intrauterine administration raises concerns about risks of pelvic infection and would require careful sterile technique for administration.

An herbal extract injected into the uterus is not a vaccine

Neem extracts need to undergo lengthy, careful trials, like any new contraceptive method; they are unlikely to be ready for use during the lag period of immunological contraceptives any time in the near future.

Apart from this dubious promotion of a new method for protection during the lag period, the problem remains of how to provide contraception during this time. The contraceptive which is used must be highly reliable because the effects of contraceptive auto-immunisation cannot be turned off. The woman will have already received an immunological contraceptive; if she becomes pregnant, the fetus will be exposed to the action of the contraceptive. The consequences of this for the development of the fetus, should she decide to continue the pregnancy or not have access to an abortion, are unknown.

A contraceptive used during the lag period should not interact with the immunological contraceptive. No one knows whether it will be possible to use hormonal contraceptives or whether women will need to rely on barrier methods to cover the lag phase. The exact duration of the lag period will vary in different women. Additionally, although HRP and Talwar use hCG as an antigen, the lag periods with their preparations are very different.

Variability of duration and magnitude of the immune response

The efficacy of immunological methods depends on the state of a person's immune system. The duration and magnitude of the auto-immune response therefore vary widely and are intrinsic characteristics of immunological birth control. Figure 4 shows four theoretically possible responses to one contraceptive formulation. The lag periods, plateau phase and waning phase will all vary and some people may never reach the threshold for effectiveness (circles), while others might conceivably find themselves sterile for life (squares). Variations occur because immune responses

depend on genetic predisposition as well as being on environmental factors, health and psychic well-being (Playfair 1989).

Immune responses depend on environmental factors, health and psychic well-being

The Indian anti-hCG contraceptive, which has undergone the most tests so far, showed a wide variation in duration of effect in healthy women. This varied from six to 11 cycles for 30 women, 12-17 cycles for 24 women and 18-27 cycles for 13 women (Talwar et al. 1992a:5). This is more than a four-fold variation between individuals. Such extreme variation does not occur with other contraceptives. How can one then rely on immunological contraceptives, particularly as the woman experiences no physical signs of changes in her immune response? HRP proposes to develop a blood prick test to check whether the anti-fertility effect has reached the effective threshold. However, testing for antibody levels will need to be available and easily accessible to all users of immunological contraceptives. This introduces administrative problems, particularly in countries with a poor provision of health services.

Around 15% of the women taking part in the trial of Talwar's prototype failed to respond to the primary refresher immunisations needed to stimulate sufficient immune response. This non-responsiveness was attributed to a recent immunisation campaign with tetanus, the carrier used in this preparation (Gaur et al. 1990).

A combination of antigens also combines their risks

Talwar and colleagues (1992:1) expect that "no single vaccine will be able to evoke a high enough response in all individuals". Their advice is to adopt a "multivaccine strategy", i.e. to develop formulations with several reproductive antigens. However, a combination of antigens also combines potential risks and the probability of interactions.

The overall failure rate of immunological contraceptives is also problematic. The percentage of women who will never mount an effective auto-immune response is likely to be relatively high because of the nature of immune reactions. USAID researcher Jeff Spieler (1987:779) warned that "a fertility regulating vaccine... would have to produce and sustain effective immunity in at least 95% of the vaccinated population, a level of protection rarely achieved even with the most successful viral and bacterial vaccines.". As table 1 (page 28) shows, a 5% minimum method failure rate is *higher* than the minimum failure rates recorded for contraceptives which are often rated by family planners as relatively ineffective: condoms, diaphragms and some natural methods.

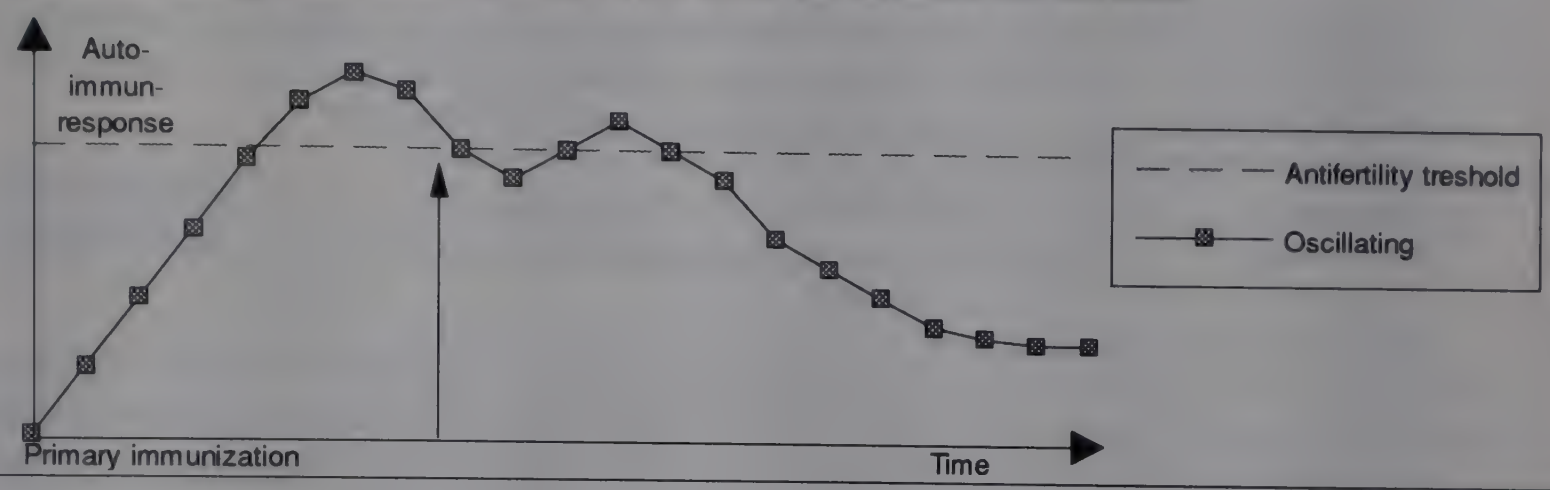
Many women developed no effective immune response

In the Indian Phase 2 trials, 20% of the trial participants never reached the threshold antibody level required (Talwar 1992b). They were therefore excluded from the trial. This is a high rate of non-responders. This procedure also reflects poor methodology for conducting clinical trials of contraceptives. The conclusions on rates of effectiveness should be drawn based on the entire group who entered the trial, not a subgroup (Holme Hansen 1989).

A person may also have a low immune response because their immune system is impaired by severe infection (for example malaria, tuberculosis, hepatitis or HIV), malnutrition or stress. Certain drugs, such as corticosteroids and anti-cancer drugs, are also immunosuppressive (Basten et al. 1991:78).

It is difficult to predict the extent of this type of low immune responses. A woman can become exposed to a disease or to greater life stresses while using immunological contraceptives. The problem of low responses caused by environmental factors is that their onset will be unpredictable. Figure 5 depicts what may happen when disease or life stress occur (arrow). The antibody titre may drop below the protective level and its contraceptive effect is not reliable.

Figure 5:
Oscillating immune response due to illness or stress



A last factor which should not be underrated is that the immune and endocrine system are complex systems which may come up with surprises (cf e.g. Rose et al 1991:130). How our body reacts to deliberate anti-reproduction immunisation is as yet unknown. The German researcher Nieschlag, for example, abandoned the idea of anti-FSH auto-immunisation for men because his test animals spontaneously resumed sperm production after three years of continuous auto-immunisation (Nieschlag 1986).

Waning phase and boosters

The point of time when effectiveness drops cannot be reliably predicted

After a certain period, the effect of immunological contraceptives wears off. This is the same process as occurs with some anti-disease vaccinations, such as tetanus, which require booster injections to maintain the protective titre of antibodies. The point of time at which the titre sinks below the effective level cannot be predicted exactly. With anti-disease vaccinations, this poses no real problem, as an approximate prediction provides adequate protection. However, this introduces new uncertainty with regard to protection against pregnancy.

A test system is needed to ensure that women know when to use additional contraceptive protection or to seek a booster injection. There are also lag phases after booster injections, although they are shorter than the lag phase for primary immunisation. Researchers suggest that this problem can be overcome by finding the minimum effective period for an immunological contraceptive and advising women to have a booster or to use an alternative method before they reach the waning phase (Griffin 1992:11).

Potential risks of frequent booster injections, including allergic reactions, are discussed in the section below on adverse effects.

Reversibility

Depending on the target antigen and the formulation, the duration of effectiveness of immunological contraceptives might range from a few months, as in the case of the current anti-hCG methods, to potentially life-long infertility. As Warren Jones stated in 1982, "The capability for reversal is an attractive but not an essential facet of any contraceptive method.... the ultimate place of a contraceptive vaccine may indeed evolve as a form of medical sterilisation." (1982:16). More recently, Griffin said that, "Vaccines with a shorter duration of effect may prove attractive alternatives to injectable contraceptive steroids [i.e. hormonal injectables], and vaccines with a longer duration of effect may be attractive alternatives to surgical sterilisation." (Griffin 1990a:508)

"Vaccines with a longer duration of effect may be attractive alternatives to surgical sterilisation"

Irreversibility is not only a safety concern, it also strongly affects the abuse potential of immunological contraceptives. This is discussed in the next chapter.

Even short-term immunological contraceptives are not reversible in the same way as other contraceptives. The effects of IUDs are reversed when they are removed. In the case of hormonal contraceptives, a woman waits until her body has eliminated the hormones and a normal menstrual cycle is re-established. Women may experience delays in the return of fertility, particularly with Depo Provera® (Guillebaud 1989). However, once an auto-immune response has been activated, the triggered changes within the immune systems take place irreversibly. As immunologist Faye Schrater points out, "immune response and contraceptive effect are distinct though related aspects of contraceptive vaccines. At best the [anti-fertility] *effect*, not the [immune] *response*, is reversible." (1992:45, emphasis added). Reversibility of immunological contraception refers to the waning of the antibody titre to a low level at which it will not interfere with a pregnancy. Once induced, changes in the immune system do not completely disappear.

"At best the effect, not the response, is reversible"

Contraceptive effects are maintained through boosting, which stimulates the body to produce high concentrations of antibodies through renewed contact with the antigen. In the case of anti-disease vaccines, boosting the immune defence is always a desired effect. Therefore it does not matter whether the immunological memory is refreshed through a booster injection with the altered antigen in a vaccine, or by contact with the germ itself.

For immunological contraceptives, however, it is crucial that the "continuing or pulsed appearance of the target antigen ... should not act as a stimulus to the ongoing immune response." (Ada & Griffin 1991c:23). For example, the appearance of sperm during intercourse must not boost the immune response of an anti-sperm vaccine because then each intercourse will elicit an immune reaction, making infertility irreversible. Refreshing immunological memory through contact with the natural antigen is called *internal boosting*. Only external boosting, based on the original synthetic antigen, should occur. In this case a woman can decide

to stop having booster injections and wait for her antibody titre to wane sufficiently to become fertile again.

The problem with immunisation against body components is that the internal antigen may be present frequently or all of the time. Non-pregnancy-associated reproductive hormones, egg cells, and sperm cells are continuously present. There is a high risk of continuous internal boosting, which could lead to life-long sterility. Anti-sperm contraceptives in women are unpredictable because boosting is dependent on coitus. The theoretical risk of boosting would be less with hCG, as hCG is only present after conception, i.e. at most once a month.

In the Indian Phase 2 trial of anti-hCG methods, the contraceptive effect was reversible, and a number of women conceived after discontinuing use of the method (Talwar et al. 1992a:5). However, whether this will be true for all women — including all long-term users — and for all types of immunological contraceptives developed, is not known. "Boosting is the great unknown", stressed endocrinologist Noel Rose at the 1989 HRP symposium (communication to the audience).

"Boosting is the great unknown"

If internal boosting can be safely excluded, it does not automatically follow that the anti-fertility effect will be reversible. Two more factors have to be considered. First, repeated use of immunological contraceptives may boost the antibody titres above the threshold for an unknown period of time. This could potentially be permanent. Secondly, even if there were no boosting at all, each individual user cannot be sure that the effect will be reversible for them. The immune system does not always work perfectly. Some people develop allergies and auto-immune diseases; these disorders are not always predictable based on past medical history or family history. They may experience "an excessive response ... resulting in irreversible infertility." (Basten et al. 1991:78). The extent of this risk will only be known during Phase 3 trials, where only people with severe diseases will be screened out.

The immune system does not always work perfectly

Switching off an immunological contraceptive: reversibility on request

Currently there is no way to interrupt an ongoing auto-immune process without creating havoc in the rest of the immune system. Griffin responded to the comment of a colleague about the lack of priority which has been accorded to the need for immediate reversibility: "The question [of] reversal on demand ... would be dealt with in the same way that you would, for instance, deal with an injectable steroid. You would inform the recipients that they would have to accept that the vaccine would be active for the stated duration of time, whether one year or two years, or however long. And you would also inform them that it is irreversible during that period." (Griffin 1990a:521).

He proposes to attempt counteracting the anti-fertility effects of anti-hCG contraceptives by administering progesterone. However, this does not interrupt the auto-immune neutralisation of hCG, it simply replaces the progesterone secreted by the corpus luteum with a synthetic or natural progesterone product. If a woman becomes pregnant while using an anti-hCG contraceptive, this may lead to a continuation of pregnancy.

However, it does not exclude potential adverse effects for the woman or her fetus. Exposure to synthetic progestins is not recommended during pregnancy because of the risk of malformations (Australian Drug Evaluation Committee 1989). "Natural" progesterone products are frequently assumed to be safer, but this assumption is based on very little evidence.

The desire to have a child is not the only reason a woman may wish to stop using a contraceptive. If a woman experiences severe side-effects shortly after an injection, such as a serious auto-immune disorder, will it be possible to switch off the immune response? She would have to wait until the effect wears out or use drugs to suppress her immune system. This lack of true reversibility is a serious draw-back of immunological contraceptives. Griffin (1990b) stated in a letter responding to criticisms of immunological contraceptives that if serious auto-immune disorders were discovered during trials, HRP would discontinue research into the contraceptives.

Immunological contraceptives "are to be used by healthy individuals who have a number of alternatives from which to choose"

Adverse effects of immunological contraceptives

"Anti-fertility vaccines are not intended to combat life-threatening or debilitating diseases, but are to be used by healthy, fertile individuals who have a number of alternative existing family planning methods from which to choose. These considerations necessitate that the assessment of safety is of paramount importance in the development of these vaccines." (Ada & Griffin 1991a:XV)

The most likely adverse effects of immunological contraceptives fall into four categories:

- ❑ auto-immune diseases
- ❑ allergies
- ❑ immune complex diseases
- ❑ disease exacerbation

Auto-immune diseases

"Vaccines to control human fertility in theory run a higher risk of inducing anti-self reactions compared with vaccines to control infectious diseases, and this risk may be greater still if powerful adjuvants are used and the vaccine is administered frequently." (Ada 1990:576)

"It is worrisome that the target of the auto-immune reactions cannot be predicted"

Nobody knows whether immunological contraceptives may lead to an immune response against body structures other than the intended antigen and thus elicit an auto-immune disease. Noel Rose and colleagues feel that "the fact that one cannot predict the target of these [auto-immune] reactions is worrisome." (1988:239). His team made tests of CTP-beta hCG in baboons and found cross reactions between hCG, striated muscle, the pancreas, and an unidentified cell type of the pituitary (ibid)

As researchers point out, the presence of auto antibodies does not necessarily mean that an auto-immune disease will develop (Ada & Griffin, 1991b:6-8). Griffin and Jones state that "It is not clear whether auto-immunity, either naturally occurring or vaccine elicited, is predictive of future auto-immune disease." (1991:186). This makes it very difficult to define who shouldn't receive immunological contraceptives because they would be more likely to develop an auto-immune disorder. Auto-immune diseases tend to be more frequent and more severe in women than men (Playfair 1989:33). There is currently no cure for any known auto-immune disease. In some cases, there are spontaneous remissions. In others, symptomatic treatment is possible. However, for severe auto-immune disease, immunosuppressive drugs such as corticosteroids are used, which may cause serious adverse effects (Playfair 1989).

"Any vaccine to control human fertility that was shown to induce auto-immune disease during clinical testing or even at the post-registration stage would be considered unsafe for general use." (Ada 1990). However, if severe adverse effects occur infrequently, they are unlikely to be detected until large numbers of users have been exposed to a vaccine. Furthermore, as is pointed out by Ada & Griffin (1991b:9). it is extremely difficult to establish a causal relationship between use of immune-mediated methods and an adverse effect.

Allergies

Allergies are exaggerated or inappropriate immune responses

Allergies are exaggerated or inappropriate immune responses. They can be caused at each subsequent exposure to an agent which stimulates the immune system. Allergic reactions can range from sizeable local inflammatory reactions at the injection site during vaccination to generalised allergic reactions including rare, but potentially fatal, cases of shock.

In Phase 1 of the Indian anti-hCG trials, 11 of 101 women (10%) became allergic to the tetanus carrier before the first booster injection. This was after one of the three primary immunisation doses (Talwar et al. 1990:302). In HRP's Phase 1 trial, two out of 30 women (6.7%) showed a delayed type of hypersensitivity reaction to the diphteria toxoid carrier which occurred after around 48 hours (Griffin 1988:187). Women considered to be at risk from allergies had been excluded from these clinical trials. These were also reactions from the primary immunisation schedule only. HRP's incidence is lower than that of the Indian trial, probably because they relied on a smaller number of injections. However, they stated that this incidence "would probably be regarded as an unacceptably high level when large-scale use of the vaccine is considered." (Griffin 1988:185)

Talwar reported that in his Phase 1 trial, "...63 subjects did not have any complaints following first injection...The remaining 25 subjects (28%) had minor complaints such as erythema, pain at site of injection, fever, oedema, generalised rash, transient joint pain, nausea, muscle pain and giddiness." (Talwar et al. 1990a:307) Some of these adverse effects are clearly signs of allergic reactions to the injection.

All women should be tested for allergies before using an immunological contraceptive

The HRP team concluded the report of Phase 1 clinical trial with the recommendation "to screen all individuals with ...[diphtheria skin] test before repeat vaccination." (Jones et al. 1988:1297,98) It will be necessary to test women before each injection to exclude foreseeable severe allergic reactions. However, this measure seems impracticable in routine family planning settings. Immunologist Schrater emphasises "Tests for hypersensitivity, or allergies, generally require a 48-hour period, thus adding another complication to vaccine use. That complication is necessary: although most allergic responses simply cause discomfort, in rare instances they can be fatal." (1992:44)

HRP is planning to use a different carrier because the incidence of allergies to the diphtheria toxoid is "almost certainly too high to be considered for wide-scale clinical use." (HRP 1988:187) The use of tetanus or diphtheria carriers in anti-hCG contraceptives, which aim at a duration of one to two years, is a cause for concern. It is known that, "immunisation, particularly with diphtheria and tetanus toxoids, may result in increasingly severe local reactions." (Cohen 1987:674) In vaccination programmes, the duration between repeat immunisation for both diptheria and tetanus has been prolonged. In the UK, for example, people are advised to avoid booster injections of tetanus vaccines at shorter intervals than five years (BNF 1989:420)

Immune-complex diseases

The most frequent immune complex diseases resulting from vaccination are lesions around the site of injection and kidney damage. This immunological hazard is caused whenever antibody-antigen complexes are not efficiently broken down and removed, but are deposited in smaller blood vessels where they cause inflammatory damage.

With anti-disease vaccines, immune-complex formation can occur at each immunisation or contact with the infectious agent. In the case of

immunological contraceptives, immune complexes may be formed when the person's body produces the natural counterpart of the antigen (for example hCG with anti-hCG contraceptives). Theoretically, the higher the concentration of the antigen and/or the more persistently it is present in the body, the higher the risk. Immunological contraceptives based on non-pregnancy associated reproductive hormones, eggs, or sperm structures as antigens are expected to be most risky.

The Indian researchers claimed that cross reactions did not lead to adverse effects

The beta-hCG contraceptives under development by Talwar's team in India and by the Population Council theoretically run a high risk of causing immune complex lesions in the pituitary gland due to their cross-reactivity with the hormone LH, which is continuously produced by the pituitary gland. The Indian and Population Council (Talwar & Raghupathy 1989:98) researchers claim that a long-term study of 60 rhesus monkeys provided a "reassuring verdict on the lack of deleterious side-effects." Griffin (1992:8), however, maintains that, "the question of long-term immunopathological or other sequelae, if any, of cross-reactive immunity to hLH is still unresolved. Resolving this issue in appropriately designed studies in relevant animal models should be a high priority for current and future research with this vaccine."

Worsening of existing disease

The adverse effects discussed above could occur in any healthy person. However, what happens if people already have a disorder of the immune system or another diseases? According to the 1989 HRP meeting the following theoretical risks exist:

- Pre-existing allergies or auto-immune diseases (e.g. rheumatoid arthritis) could be exacerbated due to the "general immunostimulation inherent in the administration of anti-fertility vaccines."
- People with a genetic predisposition towards immune disorders may develop auto-immune reactions or allergies for the first time.
- The risk of developing a chronic liver disease could be increased in persons with hepatitis B (jaundice). This includes both people with known hepatitis and those who are 'carriers' (i.e. persons who are infected with the hepatitis virus, but show no symptoms). In many tropical countries this can be a significant proportion of the population. For example, in Thailand it is around 10%.
- HIV infections might progress faster towards full blown AIDS and might increase the risk of auto-immune diseases following administration of immunological contraceptives. Moreover, the efficacy of the contraceptive would be decreased by HIV infection. (Report... 1991:289,290)

These interactions are as yet hypothetical, because so far only healthy, carefully screened people have been enrolled in clinical trials. The researchers at the HRP symposium recommended research on whether these conditions, except for predisposition to allergies, should be classified as contraindications (Report... 1991:270). These conditions are extremely difficult — if not impossible — to screen out. One cannot test for a predisposition to auto-immune diseases in a routine setting. Nor can health

care systems, particularly in Third World countries, afford the costs of HIV and hepatitis B tests before administration of immunological contraceptives.

Effects on the fetus

What happens if a woman conceives after she has received an immunological contraceptive?

What happens if a woman conceives after she has received an immunological contraceptive?

Immunological contraceptives combine two characteristics which make fetal exposure likely:

- Effectiveness is likely to be unpredictable due to individual variations in immune response.
- It is impossible to switch the contraceptives off once the immune response has been stimulated.

Interfering with the women's immune system may affect the fetus as well

Accidental pregnancy may occur either in women who develop an immune response below the threshold level for contraception or in women who reach the threshold antibody level, but experience an unexpected method failure. Damage to the fetus could be caused through a variety of mechanisms at various stages of a pregnancy. A list of potential problems was developed at the 1989 HRP meeting, including miscarriage, various visible malformations and less apparent hormonal abnormalities. Some of these adverse effects, for example "abnormalities of secondary sex characteristics, and development of possible neoplasias [cancer]" might manifest only at puberty (Report... 1991:289), as has occurred with exposure to DES (diethylstilbestrol) before birth.

During fetal development, the fetus' own immune systems develops and learns to differentiate between its own body components and foreign agents. Interference with the woman's immune system may affect the fetus as well. Long-term animal studies are needed to exclude the possibility of effects of prenatal exposure on the immune system.

Additionally, breast feeding confers immunity from mother to baby so that the baby is protected from disease for a certain period of time. Whether antibodies produced from immunological contraceptives pass into the milk and what type of effects they may have on the baby remain unknown.

Protection against the spread of sexually transmitted diseases

In the 1990s, a pertinent question about any new contraceptive is whether it will protect users not only against pregnancy but also against sexually transmitted diseases (STDs). Research on immunological methods began in the early 1970s, well before the AIDS epidemic was known.

A pertinent question for any new contraceptive is whether it will protect users against sexually transmitted diseases

The advent of AIDS is not the only change in the pattern of STDs in the last two decades. Syphilis, gonorrhoea and chancroid have been joined by new bacterial and viral syndromes associated with chlamydia, human herpes virus, human papilloma virus, as well as the human immunodeficiency virus (HIV) causing AIDS. According to HRP's 1990-91 Biennial Report: "The second generation of sexually transmitted organisms, are frequently more difficult to identify, treat and control. Moreover they cause serious complications which can result in chronic ill health, disability and death." (1992:13)

Chlamydia and gonorrhoea, two common STDs, can also lead to pelvic infection (PID) if they spread to a woman's upper reproductive organs, leading in turn to high rates of infertility and chronic pain. Rates of PID are high in some developing countries. For example, each year 1-3% of women of reproductive age in urban areas of sub-Saharan African develop PID. Village studies in India, Kenya and Uganda found rates of PID as high as 20% (Jacobson 1991).

AIDS

WHO estimated that at least 10-12 million HIV infections resulting in around two million AIDS cases had occurred globally by early 1992 (table 2, page 42). They forecast a cumulative total of 30-40 million HIV infections and 12-18 million AIDS cases for the year 2000, of which 90% will occur in developing countries. By the year 2000, a projected 80% of HIV infections will be contracted by heterosexual intercourse (HRP 1992).

We can only agree with HRP (1992:13,14) that: "the AIDS pandemic has implications for contraceptive technology. Contraceptive choices, at the individual and programme level, will have to take the risk of prevalence of HIV infection into consideration. The need for dual protection against unwanted pregnancy and against STDs/HIV poses a challenge to contraceptive development."

Immunological contraceptives will provide no protection against STDs

However, immunological contraceptives will provide no protection against STDs. There is fear that they may adversely affect the health of people infected with HIV (Report 1991:260). Furthermore, because these contraceptives depend on a functioning immune system, they are likely to be less effective in people infected with HIV or people who become infected while using the contraceptive. Because a person who is infected with HIV has no symptoms for a period which can last several years, it is highly probable that some users will be unaware that they are HIV-positive.

Table 2:
Global HIV-infections in adults, early 1992

Area	number of adult infections
North America	1 million
Central and South America, Caribbean	more than 1 million
Sub-Saharan Africa	more than 6.5 million
Northern Africa and Middle East	50,000
South and Southeast Asia	more than 1 million
East Asia und Pacific	20,000
Australasia	30,000
Western Europe	500,000
Eastern Europe and the former Soviet Union	20,000

In response to these concerns, participants at the 1989 HRP Symposium made the following recommendations:

- "That evidence of HIV infection be an exclusion criterion for Phase 1,2,3 clinical trials of antifertility vaccines".
- "That research be carried out, as a matter of priority on possible interactions between HIV infection and antifertility vaccines..."
- "That antifertility vaccines should not be considered among the preferred options for birth control in populations with a high prevalence of HIV infection, until concerns about the safety and efficacy of these vaccines in immunocompromised individuals have been resolved." (Report... 1991:260)

If recommendation three is extended to include populations in which the prevalence of HIV infection is rapidly increasing, it becomes particularly problematic. It is difficult, if not impossible, to find a population in which the spread of AIDS is not considered a concern. Even in North Africa and the Middle East, with relatively low rates of reported HIV infections, the data suggest that "extensive spread of HIV has begun in some parts of the region." (WHO 1992)

This is not the only concern. Eka Esu-Williams, head of the Society for Women and AIDS in Africa, expressed her fears at the 1992 HRP Meeting between women's health advocates and researchers, that immunological contraceptives will create an unacceptable setback to campaigns against the spread of HIV. First, injectable contraceptives are likely to contribute to the spread of HIV via improperly sterilised needles and lancets used in blood prick tests. Second, the predictable heavy promotion of anti-fertility vaccines is likely to reverse progress in the difficult endeavour to persuade men to use condoms to prevent sexual transmission of HIV.

It is a difficult endeavour to persuade men to use condoms

In its statement for the 1992 World AIDS day, WHO (1992) stressed that: "No community can afford to deny the existence of the problem of HIV/AIDS." Neither can contraceptive developers or funders of contraceptive research.

Contraceptive policies need to support public health policies

Contraceptive policies, including priorities for development of new contraceptives, need to support public health policies to decrease the spread of AIDS and other STDs. They should not contribute to more cases through administration by injection and lack of protection from transmission during heterosexual intercourse. Although this should be a priority everywhere, it is especially important in Third World countries, many of which already have high rates of AIDS and other STDs.

A far from ideal profile

As has been outlined, the immunological contraceptives which have been tested thus far are anything but reliable. They have lag periods, which involve using another contraceptive for a period of time. A woman who decides to use an immunological contraceptive will find that:

- it may take a shorter or longer time to become effective;
- she will not be able to predict exactly when the effect will wear off;
- if she is very unlucky, perhaps it will not work at all or, at the opposite extreme, she will become sterile.

These are not simply technical flaws

These are not simply technical flaws which can be solved by adjusting the formula; they reflect the inherent variability and lack of predictability of human immune responses. This lack of predictability is no problem for anti-disease vaccinations, as populations rather than individuals are the targets of immunisation programmes. Pregnancy, however, is an individual woman's concern and not an epidemic.

Less is known about safety, but concerns about risks of auto-immune diseases, severe allergic reactions, immune-complex formation and disease exacerbation cannot be dismissed.

Fetal exposure seems likely because of the unpredictability of effectiveness, the existence of a lag period and gradual waning of effectiveness, and the difficulty of switching off the immune response once a woman has been vaccinated. The effects of exposure to an immunological contraceptive on the fetus are unknown. These flaws, again, are inherent to any immunological method.

Immunological contraceptives do not prevent the transmission of STDs, including HIV. In comparison to barrier methods, especially condoms, which provide protection against infection with STDs, they provide a definite disadvantage. Wether or not immunological contraceptives will make women more vulnerable to HIV infection because their immune system is stimulated, or will interact in another way with HIV, is as yet unknown.

RISK/BENEFIT ASSESSMENT OF IMMUNOLOGICAL CONTRACEPTIVES

II. POTENTIAL FOR ABUSE

"Reproductive rights mean women's right to decide whether, when and how to have children..." (Resolution 1990)

This chapter looks at a social and political aspect of the design of immunological contraceptives which needs to be assessed in order to judge whether they provide advantages or disadvantages over existing methods: potential for abuse.

Contraceptives can enhance reproductive rights by enabling women to temporarily choose not to have children. However, if a woman is coerced into using a contraceptive against her will, the contraceptive becomes a barrier to autonomy. Contraceptive abuse has occurred in a number of countries and continues to occur. It can occur through provision without consent, sanctions against non-users, financial incentives, or refusal to remove a contraceptive on the user's request. If biased information is given to potential users to convince them to use a contraceptive this is also a form of coercive manipulation of consent. Abuse has mainly been carried out by governments aiming to reduce population growth, although there are also examples of coercion directed at minority populations within a country and at disabled women within institutions (LaCheen 1986).

The characteristics of a contraceptive determine whether or not users have complete control over starting and stopping use. In the words of reproductive rights activist Betsy Hartmann "some methods have abuse built into their design."

Three basic features are important for the abuse potential of contraceptives:

- the duration of the anti-fertility effect
- the possibility or impossibility to stop at will (user control)
- the type of delivery system or device (i.e. whether it is a barrier method, pill, injectable, implant, IUD etc.)

Any long-acting method which the user cannot stop using when he or she wants to lends itself to abuse. Table 3 shows an overview of delivery systems, duration of effects and potential for abuse for several contraceptives. Among hormonal methods, the pill has little abuse potential because its action lasts for one day and a woman can stop using it at any time. Injectables, which last for three months and cannot be reversed within this time, have a much higher abuse potential. The hormone-releasing vaginal rings currently being developed will be effective for three or six months, but a woman can remove them any time she wants. Injectables and vaginal rings thus have the same length of action, but a profoundly different abuse potential.

In the US there have been attempts at coercive administration of Norplant® involving court orders

Theoretically, the action of Norplant®, an implant which releases a synthetic form of progesterone, can be stopped anytime. However, the five year period of efficacy and the need for specialised surgery for removal give it a high potential for abuse. Following its approval in the US, there have been numerous attempts at coercive legislation involving court orders

for Norplant® use for women convicted of drug or other criminal offences and incentives for women receiving welfare payments (Alan Guttmacher Institute 1992). These proposals provide poignant evidence of the abuse potential of the method.

Table 3:
A comparison of abuse potential of contraceptives

Method	Duration of effectiveness	Possibility to stop effect at will	Delivery system/ device	Abuse potential
Barrier methods	during intercourse	can be removed by user at any time	Condoms, vaginal barrier (+ spermicide)	none
Oral hormonal contraceptives	1 day	can be stopped by women at any time	oral	low
Vaginal rings with hormones[a]	3 or 6 month	can be taken out by women at any time	vaginal slow release system	low
Injectable hormonal contraceptives	1, 2 or 3 month[b]	women must wait until the effect wears off	injection	high
Hormonal implants	5 years	can be removed at any time, but only by specially trained health workers	six capsules under the skin. Minor surgery needed for insertion and removal	high
IUDs	1 to 8 years	can be removed at any time, but only by specially trained health workers[c]	intra-uterine device, inserted and removed through the cervix	high
Immunological contraceptives[a]	potentially 1 year to lifelong	women must wait until the effect wears off	injection, oral?	high to very high

a Under development

b Return of fertility may be delayed after effect wears off

c In emergencies IUDs with a string have sometimes been removed by women themselves

Studies in developing countries have shown that women frequently face barriers to removal on request (Hardon 1993a). A Population Council study on *Service Delivery and Quality of Care in the Implementation of Norplant in Indonesia* is revealing in this regard. An Indonesian family planning manager explained, "people are told that it has to last five years, they give their word ... and rural people don't go back on their word. If they request removal, they are reminded that they gave their word". Nearly

a third of the women interviewed did not even dare to request removal because they feared the request would be refused (Ward et al. 1990; Hartmann 1991).

The abuse profile of immunological contraceptives

The effects of immunological contraceptive methods may last from one to two years, and some may prove to be irreversible. An irreversible immunological contraceptive would have such a high potential for abuse that it should not be developed. It could easily be provided without people's knowledge or consent if they believed they were receiving an injection for another purpose.

It would be very easy to administer a sterilising injection without women knowing what they receive

One to two year methods which cannot be reversed during their period of effectiveness also have a high potential for abuse in comparison to most existing methods, particularly if they are administered by injection. It is unclear at present what the final period of effectiveness of immunological methods will be; however, one to two years is the stated goal (Griffin & Jones 1991). The injectable methods currently available are hormonal methods which are effective for one month (NET-EN) or three months (Depo Provera®).

At the 1989 HRP Meeting, the social scientists Concepcion, Mundigo and Reeler (1991:239) raised doubts about whether long action was indeed an advantage. They warned: "The fact that it is administered by injection makes it easy to confuse, intentionally or unintentionally, with other preventive or curative injections... The advantage of being long lasting will be a problem instead of an advantage if the vaccine is given without the woman's informed consent...".

Immunological contraceptives may also be misrepresented as disease-preventing vaccines. Comparisons to immunisation have been used to promote immunological contraceptives. In 1978, HRP researchers stated that "immunisation as a prophylactic measure is now so widely accepted that it has been suggested that one method of fertility regulation which might have wide appeal as well as great ease of service delivery would be an anti-fertility vaccine." (Task Force 1978:360). USAID's Jeff Spieler (1987:779) reaffirmed, "Fertility regulating vaccines should be well accepted by users, given the general popularity of immunisation there would be compelling advantages for service delivery because vaccines... could be administered by paramedical and non-professional personnel, and could be integrated not only with family planning services but with other health care programmes as well."

HRP is against the provision of immunological contraceptives within vaccination programmes: "To avoid the risk of confusion and deliberate abuse...", they call for provision "either through family planning services or carefully monitored primary health care outlets but certainly not through immunisation programmes for disease control." (Griffin 1992:12)

At the 1989 HRP meeting, Concepcion and colleagues warned that: "Abuse of the birth control vaccine would not only harm family planning in general but it could also have negative consequences for public attitudes to other vaccines and to the health care system in general." (1991:240)

The description of immunological contraceptives as vaccines obscures the difference between an auto-immunisation against body structures and immunisation against disease. If users are to be fully informed about the method they are using, these differences must be made clear. Informed consent forms for clinical trials should not present immunological contraceptives as just another form of vaccination. Trial participants need to know that they are participating in an attempt to provoke a time-limited auto-immune response, and that this is a new approach not only for contraception, but for medical science. They need to be provided with a fair assessment of how risky a trial is in order to assess whether they wish to participate.

Rumours about the abuse of immunological contraceptives could have devastating effects on vaccination programmes

In India, the most advanced trials of immunological contraceptives are taking place. It may not be a coincidence that in some parts of India rumours about the introduction of "sterilising vaccines" have already led people to refuse vaccination (Bang 1992). If these sorts of rumours are fed by the misuse of immunological contraceptives in the future — even if this misuse occurs on a small scale — the consequence for vaccination programmes would be extremely serious and the spread of epidemics would be likely.

Stimulated by related animal research journalists and scientists have been led to worrisome and far reaching utopian dreams. "New animal vaccines spread like a disease", announces a New York Times headline (Browne 1991). The vaccines in question consist of genetically engineered anti-fertility antigens which are incorporated into live viruses. The oral anti-fertility 'vaccine' is then hidden in baits. Once swallowed by an animal, these viruses will spread throughout a species, just like any infectious disease. The journalist is enthusiastic:

"Biologists say that [the] new vaccines.... will provide a humane method for drastically reducing population of rabbits in Australia, rats in Indonesia, white tailed deer in the United States and other rapidly multiplying species that threaten the environment.... Since the vaccines work by immunising a female against the male's sperm, the same principle should be effective as a contraceptive in humans... American research leaders believe that within the next decade an oral contraceptive vaccine could be available for test on human subjects. A single dose, it is hoped, could confer temporary infertility for years... the method could make contraception far more accessible to residents of poor countries." (Browne 1991)

Two American researchers, John C. Herr and Roy Curtis, are collaborating on an oral anti-sperm contraceptive which incorporates the antigen into the genetic material of altered salmonella bacteria. Unlike the engineered virus described above, their product is not meant to spread. However, it *could* spread accidentally. The 1989 HRP report on anti-fertility vaccines calls for an evaluation of "the possibility of vector [i.e. bacteria or viruses carrying vaccine antigens] transmission between individuals." (Report 1991:260)

Worse than existing methods

The design of immunological contraceptives makes them likely to have a higher potential for abuse than many existing contraceptives. The development of any new technology is shaped by its historical and cultural context. Similarly, the characteristics of a technology affect both individuals and the society in which they live. Development of methods with high abuse potential can have far-reaching consequences, ranging from detrimental health impacts to erosion of civil rights. Whether actual abuse occurs depends on many factors, such as the degree of protection of human rights and the position of women within a society. In the current global political climate, we fear that abuse of contraceptives will increase.

In the current political climate abuse of contraceptives will increase

This fear does not seem exaggerated when reading scientific articles on immunological contraceptives. They contain many statements concerning the usefulness of these contraceptives to limit population growth, with the main target group described as women in Third World countries. The emphasis is on meeting demographic goals rather than the needs and rights of women to control their fertility. For example, Stevens (1986:374) states that, "... the research conducted during the past decade has brought us to the threshold of making available a new method for more effectively meeting the challenge of ever-increasing global population expansion" and Mitchison (1991:250) goes as far as to say that "To the extent that the impact of that [i.e. the demographic] crisis increases, the need for more effective family planning technologies must increase. At the very least, failure to develop something that may provide a more effective technology would be to take a grave and unnecessary risk." Many examples of similar statements exist. Characteristically, the concern Mitchison expresses about a "grave and unnecessary risk" does not refer to a risk to the health or rights of individual women.

Risk/Benefit Assessment of Immunological Contraceptives

III. Benefits attributed to immunological contraceptives

"The objective in developing fertility regulating vaccines is not to produce replacements for existing birth control technologies but to widen the choice of safe, effective, acceptable and affordable family planning methods." (Griffin 1992)

Five theoretical advantages for immunological contraceptives can be found throughout the scientific literature:

- Lack of pharmacological activity and the often attendant side effects
- Long lasting action following one or two injections
- Administration using a procedure associated with positive health benefits
- Low manufacturing cost
- Ease of delivery within existing health care services (HRP 1988:179)

No pharmacological action and side effects

This means primarily no "menstrual-cycle disturbances or other hormone dependent side-effects." (HRP 1990:27). As the report on HRP's first clinical trial points out, the lack of "discernible alterations in the menstrual cycle" would make immune-mediated contraception a "highly acceptable birth control strategy." (Jones et al. 1988:1295)

This advantage results from a comparison of HRP's anti-hCG contraceptive only with hormonal contraceptives. Within this comparison, it represents a true advantage. However, it presents no improvement in comparison to barrier methods since they also do not affect either women's or men's hormonal systems.

The advantage of having no hormone dependent side effects is not valid for immunological contraceptives that are directed against the hormones GnRH and FSH or those which lead to cross reactions against LH, such as Talwar's or the Population Council's anti-hCG formula. In these cases, side effects from disturbances of the reproductive hormones are to be expected.

Furthermore, there may be no hormonal side effects, such as menstrual cycle disturbances, but it is very likely that instead there will be adverse effects related to the immune system.

A comparison of immunological with hormonal contraceptives is interesting because of its implications. Menstrual cycle disturbances are often described as a minor inconvenience of hormonal methods. In a report evaluating the effectiveness of Norplant®, Townsend (1990) states that "While many women report irregular bleeding, these occurrences are not medically harmful." These assertions are based on measures of blood loss and haemoglobin levels, rather than studies on long-term effects of disruption of a woman's menstrual cycle. A proper assessment of the health effects and effects on well-being of menstrual cycle disturbances is needed. Not much is known about long-term effects of hormonal contraceptives in spite of their use by millions of women over a 30 year

"With hormones we are sitting on a time bomb"

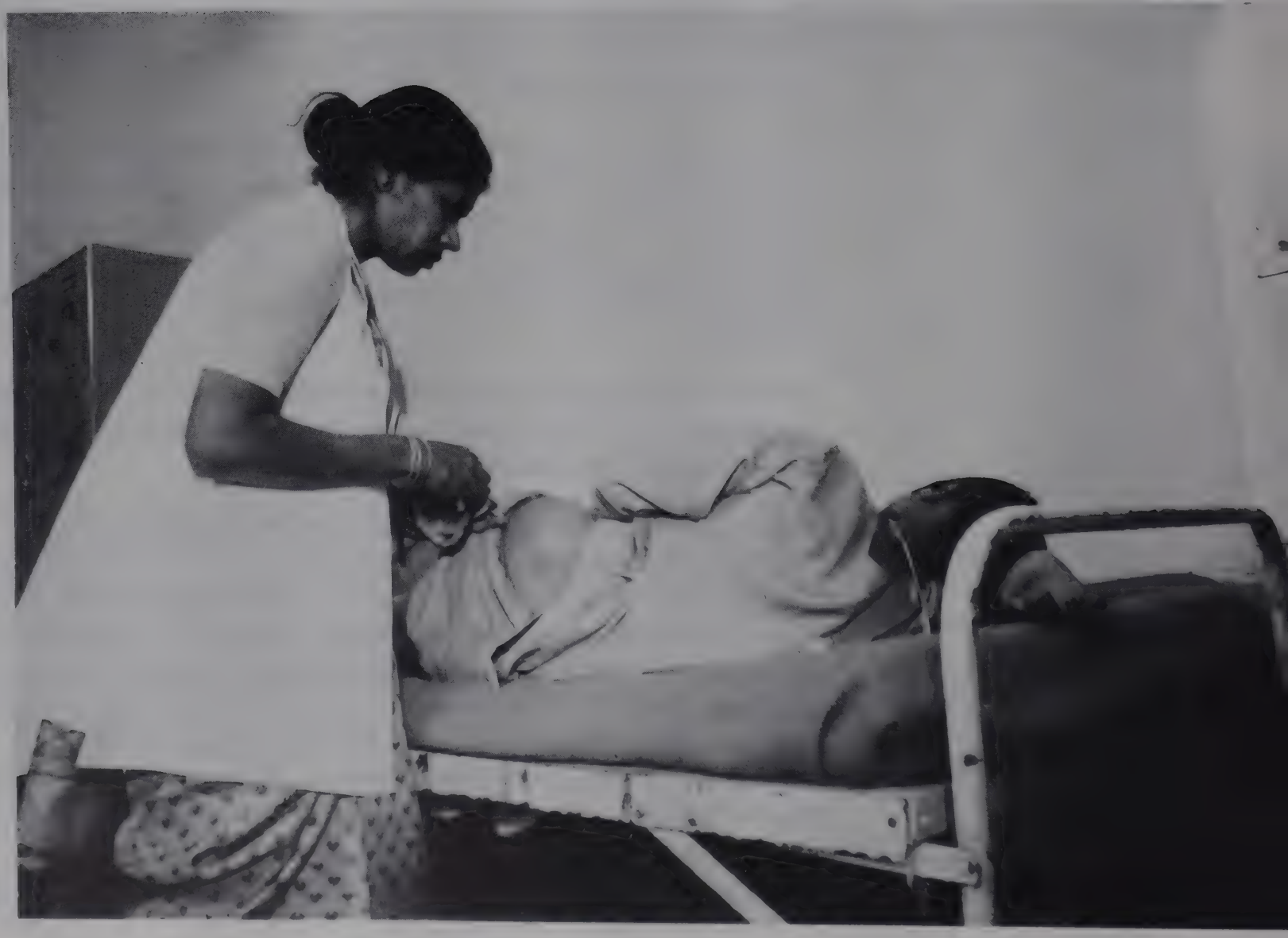
period. At the 1989 HRP symposium, one researcher stated, "with hormones we are sitting on a time bomb." (Hardon 1989). Although the "hormonal time bomb" now serves as an argument for developing immunological contraceptives, the warning refers also to them. Like hormonal contraceptives, immunological methods have a potential for unpredictable long-term effects because a complex body system is being manipulated.

Long action after one or two injections

Thus far this is only a theoretical benefit because the immunological contraceptives tested so far do not provide the long duration of effect required after one or two injections. The current anti-hCG contraceptives are unable to reach the stated goal of one to two year efficacy and are only effective for approximately six months. Talwar's anti-hCG vaccine requires three different injections.

The need for several injections for primary immunisation increases the risk of incomplete protection against pregnancy since some women may not get all injections. Yet, "an immunization schedule which is only partly successful may run the risk of inducing fetal damage or incorrect development." (Ada & Griffin 1991c:22)

The increase in potential for abuse is linked to long action as is discussed above. One argument in favour of long acting contraceptives is that they are convenient for women and that they allow a more spontaneous sexuality because they are coitus independent. On the other hand, women



have no or little control over these contraceptives and cannot stop their effects at will. In a survey on provision of Norplant®, a five-year method, in Finland, providers described the long period of effectiveness as a disadvantage because "the moods of Finnish women change quickly", as one doctor remarked (Ollila et al. 1993).

Administration method associated with positive health benefits

This advantage refers to the "acceptability of the 'vaccine principle'- [which is] of particular importance in developing countries." (Jones 1986:184) It is closely connected with the fifth advantage of "ease of delivery within existing health care structures."

The comparison with vaccines may provide benefits to administrators who would like a new type of contraceptive to be accepted easily. However, it also highlights three interconnected risks: misinformation about the nature of the immunisation, abuse potential, and negative impact on participation in vaccination programmes.

Low manufacturing cost

Experts at the 1989 HRP Symposium estimated that the cost of one dose of an anti-fertility vaccine would be comparable to modern genetically engineered vaccines such as the hepatitis B vaccine. If a new technological approach such as timed-release microspheres is used, the price will probably be higher. The eventual price will also depend on how risky particular types of immunological contraceptives are. The cost of liability insurance could cause an increase in price (Beale, communication to the symposium). Like Norplant®, long acting immunological contraceptives could present a problem of *affordability* to users if the cost for years of contraceptive coverage must be paid at a single time, rather than being paid by the month (like the contraceptive pill) or by small boxes (like condoms). Whether immunological contraceptives will be low cost for family planning programmes and users is unclear at present. If there is a need for repeated boosters and tests for antibody titre levels, administrative costs will be relatively high.

Subsidies obscure the real cost of a contraceptive method

Contraceptive provision is subsidised by foreign development aid in many Third World countries. These subsidies obscure the real cost of provision of a method and may divert resources from more cost-effective health care. When the United Nations Population Fund (UNFPA) stopped subsidising Norplant® distribution in Thailand, the government decided to provide Norplant® only to selected groups, such as hill tribe and Muslim women, because of its high cost (Richter et al. 1993:86,87). Not only does this strategy raise concerns about population control in ethnic minorities, but it means that the earlier training programmes for Norplant® provision in many parts of the country was a waste of resources because the doctors who were trained will not provide Norplant®. In retrospect, the time could have been better used for training in some other aspect of medical care which would have had a real impact on people's health. This example highlights the need to consider full costs, including training costs, costs for adequate medical care and long-term costs when subsidies are no longer provided, including the cost for long-term follow-up of users.

The calculation of low cost also omits the question of the costs of development of new contraceptive methods, much of which comes from public sources. Agencies such as the WHO's HRP, the Population Council and USAID's CONRAD research programme are currently investing around 10% of their total contraceptive development budget on anti-fertility vaccine research (Spieler 1992).

Ease of delivery

Thau praises the contraceptive vaccines for having "little need for clinical support." (Mauck & Thau 1990:131) And Griffin (1991:189) feels that "The successful development of safe, effective and acceptable vaccines of this type [i.e. beta-hCG-CTP with only a single injection] will be particularly beneficial to both the users and providers of family planning methods in those countries where the storage and distribution of drugs and devices is difficult and access to health services is limited."

The idea of immunological contraceptives as methods for easy mass administration is misguided

The idea of immunological contraceptives as methods for easy mass administration is misguided. A client-centred contraceptive delivery system should first ensure a free, informed choice of methods and then ensure their appropriate and safe use. Methods which are long-acting and not reversible on demand require more careful delivery and more attention to pre-provision counselling than user-controlled and fully reversible methods.

The immunological mode of action makes delivery complex for several reasons:

- the need for medical examinations to exclude certain diseases and pregnancy;
- the provision of another contraceptive during the lag and waning periods;
- repeated testing of antibody titres:
  - to find out when the lag period is over and the contraceptive has begun to be effective and when its effectiveness has started to wane;
  - to find out whether infections, malnutrition or stress depress the immune response;
- the need to ensure that the primary immunisation schedule is followed, and that booster immunisations are given at the appropriate times;
- careful medical follow up.

Repeated clinic visits will be necessary

Some technical problems may be ironed out as this research progresses. However, immune response varies between individuals and follows a pattern of gradually building up to an effective level and gradually declining. These characteristics of immune responses will not change, no matter how much the technology improves. Immune response is also inperceptible: a woman has no sensations to tell her if her immune response is high enough to protect against pregnancy; she will need a blood test to know. Therefore, repeated clinic visits will probably be necessary even if a contraceptive requires only one primary injection. It will also continue to be necessary to identify people with contraindications to immunological methods.

Summary

To sum up an assessment of the five arguments in favour of immunological contraceptives:

❑ *Lack of pharmacological activity and attendant side effects:*

Some immunological side effects, such as allergic reactions, are likely. Serious effects, such as auto-immune reactions, cannot be excluded. The mode of action is immunological rather than pharmacological. This is a new mode of action and safety must be carefully assessed.

❑ *Long lasting action following one or two injections:*

Not technically possible at present with the anti-hCG formula; may be a negative quality if it becomes possible, as it makes abuse more likely and increases health risks for the user and the fetus (if accidential pregnancy occurs) because the action of the contraceptive cannot be "switched off".

❑ *Procedure associated with positive health benefits:*

Misleading comparison with anti-disease vaccines has already occurred in clinical trials; this is a serious concern.

❑ *Low manufacturing cost:*

Costs unknown at present, but are likely to be high if costs for appropriate delivery are considered. Costs may increase if microspheres are used to avoid the problems associated with a complex immunisation schedule and too short a length of action;

❑ *Ease of delivery within existing health care services:*

Unlikely at present; repeated tests for antibody titres and health checks appear to be necessary.

PRINCIPLES OF RESEARCH AND ETHICAL STANDARDS FOR IMMUNOLOGICAL CONTRACEPTIVE RESEARCH

"Doctors should cease any investigation if the hazards are found to outweigh the potential benefits." (Declaration of Helsinki)

This chapter examines the principles researchers have agreed upon for immunological research and whether these standards are being met. It also looks at the conduct of trials and whether they follow international standards for ethical research involving human beings, as set out in the Helsinki Declaration of 1964 [last revised in 1989] (CIOMS & WHO 1993)

In 1977, the Human Reproduction Programme (HRP) of WHO convened a meeting of a number of immunologists, reproductive biologists and representatives of drug regulatory authorities to define standards for the development and testing of immunological methods. The participants specified four "principles for the development of anti-fertility vaccines":

- To be effective, the target antigen should be essential for the reproductive process.
- To minimise the risk of auto-immune disease, the target antigen should be restricted to the intended target.
- To minimise the risk of immune-complex disease, the target antigen should not be present continuously in the vaccine recipient but only intermittently and/or in low concentrations.
- The anti-fertility effect of immunisation should not be permanent and there should be no demonstrable hazard to offspring born subsequently to users (as summarised in Ada & Griffin 1991a:XVI)

In 1989, after the completion of Phase 1 clinical trials of the Indian and HRP anti-hCG formulas, HRP called a second meeting. This time they also invited lawyers, social scientists and consumer representatives. Beyond the review of the principles of antigen selection and discussion of further trial phases, they intended to discuss "social, legal and ethical issues which the preparation and use of these vaccines would raise so that appropriate action could be taken to avoid potential problems in this area." (Ada & Griffin 1991a:XVII)

The third principle defined in 1977 was changed at the 1989 meeting to "*Preferably*, the molecules should be present transiently and in relatively low amounts so as not to overwhelm the predicted immune [antibody] response" and was re-classified as an "efficacy criteria" (Report... 1991:254, emphasis added). The earlier principle was much stronger: all methods targeting the continuously present non-pregnancy associated hormones and hCG-prototypes cross reacting with LH would have been excluded from development.

Seminar participants continued to express their concerns about using continuously present hormones as targets. Endocrinologists Chard and Howell re-affirmed that "on the basis of the animal evidence... *all* of the hormones of the hypothalamic-pituitary-gonadal axis [i.e. GnRH, FSH and oLH] would be excluded." For them, the hCG-CTP continues to be "the only significant candidate for an anti-fertility vaccine for the foreseeable

future." (Chard & Howell 1991:111, original emphasis) The final report of the seminar also stresses that "the unknown consequences of chronic immunity to 'self ' molecules in the brain, pituitary and gonads would argue against using immunogens restricted to these sites." (Report... 1991:255)

Meanwhile, human trials with formerly unacceptable target antigens are in full swing

Three years later, human trials with these formerly unacceptable target antigens are in full swing. The Population Council and the National Institute of Immunology are investigating anti-GnRH contraceptives in men. The Indian researchers are testing anti-GnRH methods in women "to prolong post-partum amenorrhoea" and anti-FSH methods in men. The main researchers from both institutes, Rosemary Thau and Pran Talwar, were participants at the 1989 Symposium. How do they justify the research?

So far, the US Food and Drug Administration (FDA) has not permitted clinical trials on an anti-GnRH formula as a contraceptive, but only as a treatment for prostate cancer. In India, however, Talwar tested an anti-GnRH contraceptive on women who had just given birth. Fellow researchers at a 1992 HRP meeting openly condemned this research. What if the infants were exposed to the anti-GnRH antibodies through breast milk? Infants and nursing women are particularly vulnerable groups in whom research is allowed only under very restricted circumstances. And why would women need a special immunological contraceptive for the post-partum period when "breast feeding [on demand] provides more than 98% protection from pregnancy in the first six months"? (HRP 1990:65)

The fourth principle of 1977 that required the contraceptive effect to be non-permanent was reaffirmed at the 1989 Symposium. However, the statements of individual researchers contradict this consensus, leading to concerns that immunological contraceptives which do not conform to these norms may be developed. According to Rosemary Thau, "some vaccines may [even] be designed to be used as non-surgical means of sterilisation." (in Mauck & Thau, 1990:728)

Testing a contraceptive for humans in baboons is unlikely to yield meaningful data

Standards for adequacy of animal trials

According to Griffin and Hendrickx (1991:32), the evaluation of safety, reversibility and effects on offspring of any beta-hCG formula in baboons is "unlikely to yield meaningful data in terms of direct or indirect interference with hLH production and/or function." (Report... 1991:261) Baboons produce their own chorionic gonadotrophic hormone (bCG, baboon chorionic gonadotrophic hormone), which is different in structure and in its exact secretion profile from the human form, hCG. If baboons are immunised with human beta-hCG, this elicits a very poor reaction against bCG and does not elicit any cross reactions with baboon LH. Testing the human hCG-formula in baboons thus has no predictive value for the most important potential risks, namely the risks caused by cross reaction with LH.

Until the 1989 Symposium, HRP researchers stated that they needed to develop and test a specific baboon analogue of the human CG antigens in order to carry out tests in baboons which would be more predictive. This was to be a precondition for Phase 2 clinical trials (HRP 1989:188-190).

"You should not think we haven't tried"

The plan has been quietly dropped. "You should not think we haven't tried" said Griffin at the 1992 HRP Meeting, adding that HRP had spent more than US$ 200,000 on the project. However, Stevens stated that they hadn't tried enough and that such a trial was still needed (personal communication).

The French researcher Bellet, who is working independently of the major research teams, announced palns to skip the test phase in monkeys altogether and to pass directly from rats and rabbits to women "Because of the great safety" of his synthetic anti-hCG formula (Joras 1992:8, Schneider 1992).

The first principle of the Helsinki Declaration of the World Medical Association stresses that human trials should not be carried out unless appropriate animal trials have already been conducted in order to protect participants in trials (CIOMS & WHO 1993).

Standards for prevention of abuse

At the 1989 HRP meeting, the working group on "social, ethical and regulatory aspects of antifertility vaccines" stressed that "potential risks and benefits of antifertility vaccines need to be assessed from the biomedical viewpoint as well as from the viewpoint of potential misuse and abuse." (Report... 1991:290)

The role of this group should have been to map out strategies to minimise the risk of political abuse. Yet, nothing seems to have been farther from the mind of the chairperson of that group. "Clearly the vaccine will be abused", said J. Dunne, who then proceeded to tightly control the debate. Controversies were cut short and participants were admonished to use "positive" language.

Participants were admonished to use "positive" language

The final published version of the report reassures the reader that "abuse risks associated with antifertility vaccines are the same as those that apply to all methods of birth control." The only proposals to deal with the question of administration of the vaccine without the consent or knowledge of the recipient are to keep the contraceptive vaccines apart from anti-disease vaccines in order to avoid confusion and to study the health care requirements needed for the appropriate use of the antifertility vaccines (Report... 1991:292)

According to Mitchison (1991:249), there were "sharply contrasting points of view" at the 1989 symposium: "Some regard it [the anti-fertility 'vaccine'] as tampering with germ cells and the complexities of the immune system, and therefore extremely dangerous... Some hope for a vaccine simply because it will provide women with a worthwhile new birth control option, while others hope that it will provide an unprecedented effective instrument of demographic control."

Ethics of clinical trials

Are clinical trials of immunological contraceptives being carried out according to international standards? In their background document on clinical trials for the 1989 HRP meeting, Jones and Beale (1989)

The number of blood samples taken during clinical trials "would be untenable in anaemic Indian women"

advocated variations in the design of Phase 1 clinical trials to "accommodate unavoidable geographic and cultural logistic difficulties and to avoid an unacceptable imposition on the health status of volunteers." For example, they referred to the number of blood samples taken during clinical trials in Australia, and concluded: "this would be untenable in anaemic Indian women." In the published version of the report, this sentences was changed to "such extensive sampling schemes might be inappropriate in other populations." (Jones & Beale 1991)

Were anaemic women recruited for Indian Phase I trials? Normally, Phase 1 trials should be limited to healthy volunteers. According to Talwar (pers comm 1989), in India 90% of the women are anaemic and their immune status is far below the one of Western counterparts. It is unclear whether he limited his Phase 1 trials to healthy women.

Before HRP entered clinical trials, Jones warned that "the seriousness of any of the potential hazards, and the recognition that a fertility regulating vaccine is an entirely new contraceptive principle, dictate extreme caution in proceeding to clinical trials." (1982:17)

There had already been considerable controversy because of unethical trials in India. An Indian scientist reported in *Nature* that: "Although Talwar was the first to put the hCG vaccine into human trials in 1974, he lost the race because of controversies that cropped up after he jumped the gun. In a hurry to beat his competitors, he vaccinated six unsterilized women with hCG-TT [tetanus toxoid] vaccine when its efficacy was still in doubt. Two of the women became pregnant, the World Health Organisation withdrew support and questions on ethics raised by the Indian scientific community forced him to go back to the laboratory and animal trials." (Jayaraman 1986:661).

This research was clearly unethical because of the lack of animal data on potential teratogenic effects.

Talwar complained that HRP's own interests had prompted it to withhold further funds and that this was a plot by Western scientists to undercut successful research by Third World researchers (Tripathi 1979). Times have changed. By 1993, Talwar is again at the forefront of anti-fertility vaccine research, and an advisor to HRP's Steering Committee for the Task Force on Vaccines for Fertility Regulation (HRP 1992:146).

The researchers continue their race for an anti-hCG contraceptive

The Indian and the HRP team continue their race for an anti-hCG contraceptive. Mitchison (1990:726) even expressed his worries about the known cross reactions between the Indian product and LH and about the risks of the "drastic" immunopotentiators used in HRP's formula - but then concluded: "That concern diminishes as the number of women who have been vaccinated without adverse consequences increases."

This is a shift in the most fundamental logic of clinical trials. The onus should be on researchers to ensure that there appears to be an acceptable risk benefit balance *before* human trials are carried out. According to the Declaration of Helsinki (CIOMS & WHO 1993):

"Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits...." (Fifth principle)

"Concern for the interest of the subject must always prevail over the interests of science and society." (Declaration of Helsinki)

This means that only after a thorough review of the available theoretical knowledge and "adequately performed laboratory and animal experimentation", are researchers allowed to start clinical trials. These trials should be carried out only if the "importance of the objective is in proportion to the inherent risk to the subject", whereby the "concern for the interests of the subject must always prevail over the interests of science and society." (Declaration of Helsinki, principles 1,4,5,) (CIOMS & WHO 1993)

Are women informed about the unreliability of immunological contraceptives and the questions about safety and reversibility? How are women convinced to participate in these trials? Scenes of enrolment in Indian trials were documented by German film makers (Schaz & Schneider 1991). These scenes are very disturbing. One women was told:

"We have got a new injection... the effect of the injection stops children for one year... You need not be afraid about this. The injection has no side effects. You see this injection is absolutely 100% effective... we'll also put in a copper-T [an IUD; for use during the lag period]. Continuous copper-T is not very good. If you have it 3 years, 6 years, then there is the risk of cancer. That's why we want you to change..." (Schaz & Schneider 1991).

The physician complained of feeling insufficiently informed about the risks and benefits of the test product

Then the women are asked to sign a consent form in English, although "only a few of the women can understand and read English" (Schaz & Schneider 1991). The film maker was told by a physician that this type of enrolment was no exception. The physician even complained of feeling insufficiently informed about the risks and benefits of the test product herself.

The quality of the informed consent procedure varies between the research teams. HRP, for example, has designed a comprehensive information form in lay language, which unfortunately is still not publicly available.

Informed consent

One of the principles of true informed consent is the assurance that the trial participant "is free to withdraw his or her consent to participation at any time" (Declaration of Helsinki) (CIOMS & WHO 1993). With immunological contraceptives this is not possible since contraceptive effect and potential adverse effects may continue for a considerable time after withdrawal from the trial. For meaningful consent, the women should be informed about this.

Participants of HRP's symposium in 1989 explicitly recommended, "that upon registration, a detailed free and informed consent procedure outlining the particular features of the new method be developed, appropriately updated and used consistently." (draft of the report:6) Whereas in the draft report this recommendation was placed on page six, in the published report it was placed between two paragraphs on clinical trials, where it

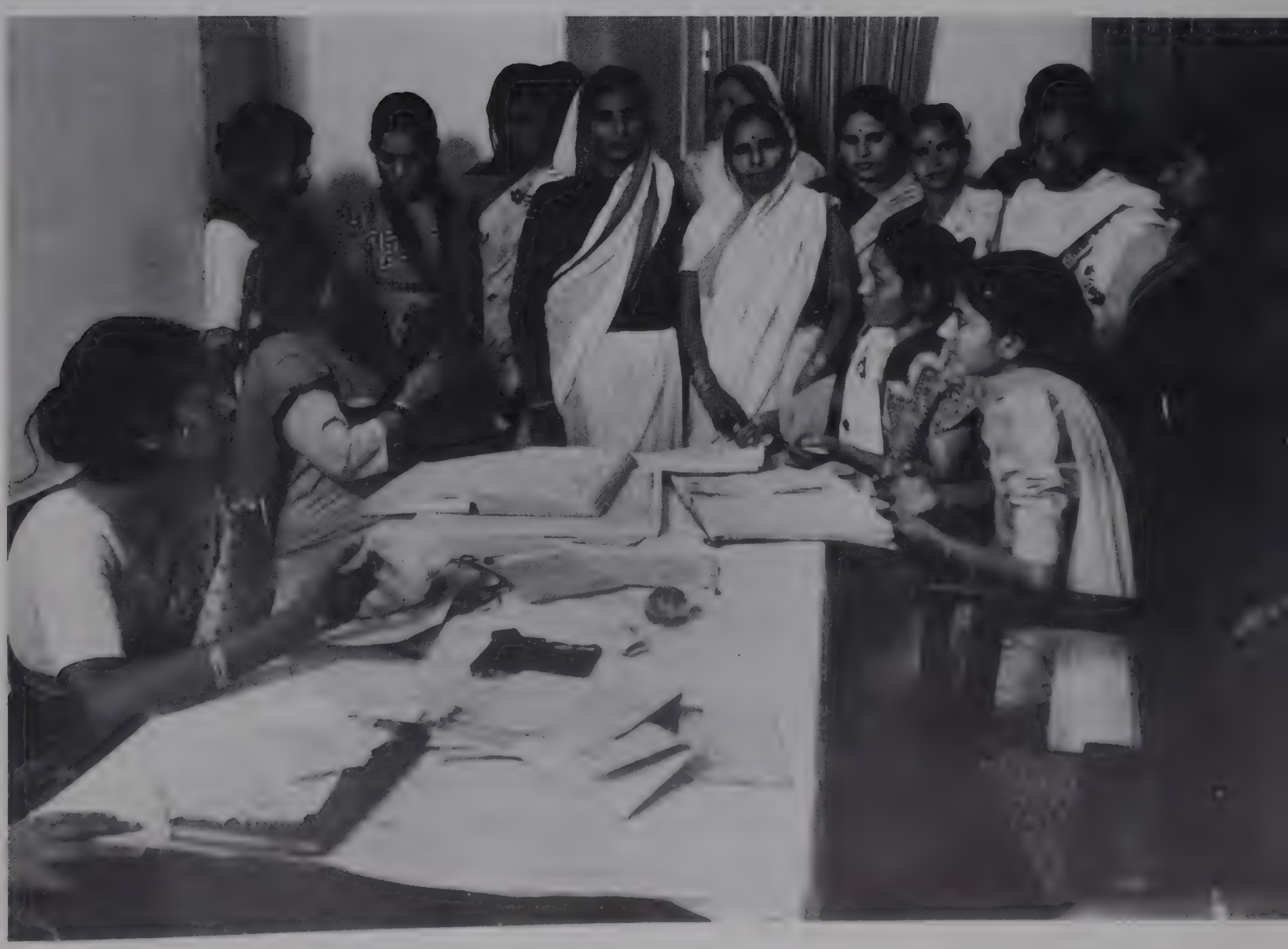
looks like a recommendation for clinical trials, and not for use after registration (Report... 1991:294).

Women should sign an informed consent form before using an of an immune contraceptive

However, participants of the symposium explicitly recommended an informed consent procedure for all users of immunological contraceptives and also for post-registration use. Unfortunately, this was not made clear enough in the published report.

Familiy planning programmes generally do not require clients to sign informed consent forms before receiving a contraceptive. There are a few exceptions; for example this is required for IUD use in the USA. Such a recommendation indicates a higher potential for abuse with immunological contraceptives and concern about unknown long-term health risks. Although an informed consent form cannot prevent coercive use, it might indeed deter casual administration of immunological contraceptive methods.

Such a document would also provide evidence of administration for women undertaking liability suits. For example, the manufacturer of the Dalkon Shield IUD, AH Robins, settled thousands of claims from women harmed by the Dalkon Shield after having been found guilty of knowingly selling dangerous devices. However, most women from Third World countries who might have been able to claim were unable to do so. They were unable to obtain proof of insertion of this IUD due to inadequate medical records (Akhter 1989, pers comm).



Are researchers following their own standards?

Although immunological contraceptive researchers have proposed a set of principles for this research, not all investigators are following these principles. In particular, a large part of the research is directed towards target antigens identified as inappropriate because they are continuously present in the body.

For some researchers the desire to improve safety, reliability or user control clearly is not a prime motivation

For some researchers the desire to improve safety, reliability or user control clearly is not a prime motivation. Mitchison (1990:612), for example, encouraged the researchers at the 1989 CONRAD International Workshop on anti-egg and anti-sperm contraceptives:

"I want to re-emphasise that finding good candidates [antigens] is relatively cheap compared with the enormous cost of developing and testing a vaccine. This argues against going for broke at too early a stage. But, on the other hand, funding is competitive, and the earlier we have something to show for our efforts, the more likely we are to secure further support. In this sense a prototype vaccine is needed, even though we know that it may not be the optimal choice and may never enter widespread use."

There are questions about whether appropriate animal models have been used in trials of anti-hCG contraceptives. Some human trials of immunological contraceptives are clearly unethical; for example an early trial of an anti-hCG contraceptive in India on unsterilized women and a trial of an anti-GnRH contraceptive on breast feeding women. Some of the principles adopted in the Declaration of Helsinki are beeing ignored or only partially followed. Immunological contraceptive researchers are not fully adhering to the set of principles for this research which they agreed upon in 1977, some of these principles have been weakened over time. In the race for research funds, are standards for safety set aside?

Immunological Contraceptives: Miracle or Menace?

"I think it would be a boon to our family planning programme if such a vaccine is introduced with all the safety precautions. And then I think the population of India will be brought under control very fast — I think that will be a dream."
(Dr. Karande, in Schaz 1991)

Immunological contraceptives are based on a completely new mode of action. They intervene in a complex body system which normally does not attack the body's own components, but acts effectively against intruders. The aim of immunological contraception is to get the body to produce a targeted auto-immune response, the effect of which is limited in time, and which is medically harmless. A range of immunological contraceptives are being developed to attack hCG, GnRH, FSH, sperm or the mature egg cell. Only the anti-sperm contraceptive for women does not incite the body to attack one of its own components; all of the others have an auto-immune effect.

This new principle of contraception has been the subject of research for more than twenty years. In the eyes of the researchers, immunological contraceptives promise five advantages:

- no pharmacological activity and hence no disruption of the hormone system
- a long effective period
- a positive health image from vaccination
- cheap to produce
- simple to distribute.

Immunological contraceptives do not live up to these promises. Instead of being pharmacologically active, they are immunologically active, which is also likely to cause side effects. A large part of the research is aimed at affecting reproductive hormones which form part of a complex and interdependent hormonal system. The duration of action of immunological contraceptives is expected to last from one to two years. At present a six month effective period requires more than one injection. Various tests will be needed before and after administering an immunological contraceptive. A second contraceptive will be needed during the lag period. Administration of immunological contraceptives will not be simple, nor will they be inexpensive when the true costs, including costs for appropriate delivery, are calculated. The fact that vaccinations generally have a positive image is not so much an asset of the contraceptive itself as an advantage for its promotion.

What do we expect from a new contraceptive?

In our view, a new contraceptive should meet the following minimum requirements:

- It should be effective as a contraceptive and should not pose health risks nor unacceptable adverse effects to the user or to children who are accidentally exposed before birth because of contraceptive failure.
- It must offer significant advantages over existing contraceptives. Otherwise, its development is not justified and research and

development costs will be wasted and people will be subjected to unnecessary risks (Declaration of Helsinki) (CIOMS & WHO 1993).

- ❑ It should offer protection against AIDS and other STDs? This is a concern everywhere, but especially in countries with a high current or projected rate of HIV infection.
- ❑ A contraceptive should not interact with conditions such as anaemia, malaria, other infections by becoming either less effective or riskier.
- ❑ It should not have a high abuse potential.

Reliable and safe?

The list of adverse effects that researchers believe to be likely is disturbing

Based on the current research results and on the nature of immune responses, immunological contraceptives are unlikely to provide protection against pregnancy during the entire period of use. A lag period will exist during which the immune response gradually builds up, and also a phase during which the effect gradually wanes. Without additional tests, a person will not know whether she or he is protected, because the length of the lag period varies between individuals. Even during the phase of contraceptive effectiveness, there could easily be a decrease in the number of antibodies present, for example when the immune system is weakened by other factors such as malnutrition, illness or emotional stress.

Not all users will attain the required antibody level; in some, the auto-immune response could turn out to be too weak to prevent pregnancies. There is also a risk that some users will develop an unusually strong response and remain infertile for the rest of their lives.

The adverse effects which could appear either short term or long term are not yet known. They may involve disturbances of the immune system and potentially disturbances of other regulatory systems such as the hormonal system. The list of side effects that researchers believe to be probable at this early stage is long and disturbing enough to cast doubts on the principle of immunological contraception.

The unreliable and complicated profile of effectiveness makes it highly probable that women will have unwanted pregnancies due to contraceptive failure. If this occurs, the consequences for the fetus are unknown. Clinical trials and animal tests can only provide partial information about these effects, particularly if they are subtle, rare, or do not occur until exposed children reach puberty.

Advantages over other contraceptives?

The condom has already four out of the five advantages attributed to immunological contraceptives

Out of the five advantages claimed for immunological contraceptives, four are already displayed by another contraceptive: the condom. The condom does not disrupt the hormonal system, is easy to distribute, cheap to produce and has a fourth *real* advantage for health (as opposed to relying on the positive image of vaccinations), since it reliably protects against the transmission of STDs and AIDS. Nor do other contraceptives fare badly in comparison. Most are immediately reversible upon discontinuing use; only hormonal injectables have an action which cannot be stopped during the period of contraceptive effectiveness. An auto-immune response is irreversible and its duration unpredictable.

Do immunological contraceptives have a potential for abuse?

The goal of research into immunological contraceptives is to produce a contraceptive which is administered by injection or as a single, long-acting oral dose. The design makes abuse easy in comparison to most other methods, as administration could occur without comprehensive counselling, without the necessary diagnostic examinations and even without the consent of the person concerned. A person who has received an immunological contraceptive is subject to its effects until the period of effectiveness is over.

Even during clinical trials, there have been instances of women being misinformed or receiving incomplete information and, contrary to ethical norms, an immunological contraceptive has been administered to nursing mothers. How much greater is the probability of abuse when immunological contraceptives are used on a large scale following registration?

These fears arise in part from the goals of the organisations who are carrying out or are funding the research. Many of the researchers' and funding agencies' statements indicate that the development of immunological contraceptives is at least partially motivated by the search for more effective controls over population growth. From this perspective, long duration of action and provider-dependency are advantageous. For population programmes and family planners, contraceptives which are not administered by users themselves have the advantage that there is no risk of "user failure", i.e. pregnancies due to incorrect use which may either happen voluntarily or involuntarily.

Contraceptives which cannot be discontinued by the user herself have an advantage from the population control perspective

In immunological contraceptives, low rates of user failure may be accompanied by a high risk to users and offsprings. However, if one believes that the birth rate of a whole population poses a risk, as does Mitchison, chair of the 1989 HRP meeting on immunological contraceptives, then the risk to an individual woman may not weigh very heavily in comparison.

Current political and economic conditions are grim in many parts of the world. National governments are under pressure from industrialised countries and international organisations to implement population control programmes as a precondition for loans or foreign aid. As a result, coercive use of contraceptives is likely to continue to occur. In these circumstances, a "vaccination against pregnancy" represents a potential danger to health and people's health and rights.

Is provision easy?

Medically safe provision of immunological contraceptives is unlikely to be cheap for a family planning service. Proper administration of an (ideal) immunological contraceptive would consist of at least the following steps:

- Extensive counselling on the mode of action and potential risks and on the impossibility of stopping the contraceptive during its period of action, as well as information about available alternatives.
- Pregnancy testing (or administration during menstruation).

- ❑ Tests for contraindications, which, on current knowledge, must include at least HIV, risk of allergies or auto-immune conditions, hepatitis B infection and malaria.
- ❑ Where there are no contraindications, obtaining written informed consent.
- ❑ Selection of a second contraceptive for the lag period.
- ❑ Administration of the injection using sterile equipment (or administration of an oral product, if this is developed).
- ❑ Towards the end of the lag period, one or more tests to determine whether an effective antibody titre is present. These are blood tests, so equipment must be sterile.
- ❑ Where wanted, booster injections after the end of the minimum period of effectiveness and antibody titre tests to see whether the booster has been effective.

The administration of an immunological contraceptive is complex

The administration of an immunological contraceptive is complex. Many health centres do not have the facilities to carry out extended diagnostic work. Given the limited health budgets of many poor countries immunological contraceptives are likely to be administered under inadequate and unsafe conditions.

The effects of malnutrition, anaemia, and many infections on the immune responses required for contraception are not known. If a person develops a condition which weakens their immune response while using an immunological contraceptive, they will have no outward sign that their contraceptive has become ineffective until pregnancy occurs.

And still the research goes on

There are inherent problems associated with an immune response (lag period, titre fluctuation, adverse immunological effects). It is foolhardy to stimulate an unnatural response in as complex a system as the immune system. Immunological contraceptives, in most cases, interfere with the production and action of reproductive hormones. The history of hormonal drugs has already shown that long-term and unpredictable effects can occur over more than one generation when a complex body system is disturbed. Even researchers doing this research are no longer convinced of the safety of immunological contraceptives.

The way the research is being carried out is questionable

The way the research is being carried out is in itself questionable. Not all the necessary animal tests have been conducted. Some scientists are deliberately developing immunological contraceptives which lead to cross reactions with other endogenous substances, and which have been rejected by other researchers. Women have been persuaded to take part in clinical trials without proper counselling. There is competition among research teams to develop the first market-ready product. The need to demonstrate results in order to acquire further funding has determined research priorities. For example, because US funding was not available for post-conception methods for political reasons, some research teams turned their attention to pre-conception methods involving greater risks of adverse effects, such as anti-sperm, anti-egg, anti-FSH and anti-GnRH methods.

This study has shown

- that immunological contraceptives are unlikely ever to be sufficently reliable;
- that adverse effects are likely to occur, some of which may be serious;
- that lack of reversibility during use and the mode of administration of these agents facilitates abuse;
- that existing contraceptive methods provide better alternatives.

This research should not be continued

From the perspective of the user, it is difficult to justify this research. The induction of an auto-immune reaction is a totally new mode of action for a contraceptive, with a potential for new and unpredictable adverse effects on the user and on any children born with exposure to the contraceptive. Immunological contraceptives will be easier to use coercively than most existing methods if researchers meet their goals for long action and easy administration. No protection against transmission of STDs is offered.

Unless concerns about safety, effectiveness, predictability, reversibility and potential for abuse can be met, this research should not be continued. Unless a clear advantage can be shown over existing methods, human trials cannot be justified.

ABBREVIATIONS

CONRAD	Contraceptive Research and Development
CTP	carboxyterminal peptide
DT	diphtheria toxoid
FDA	Food and Drug Administration (of the United States)
FSH	follicle stimulating hormone
GnRH	gonadotrophin releasing hormone
hCG	human chorionic gonadotrophin
HRP	Human Reproduction Programme (of WHO) which is short for: Special Programme of Research, Development, and Research Training in Human Reproduction
IUD	intra-uterine device
LH	luteinising hormone
NICHD	National Institute for Child Health and Development
NII	National Institute of Immunology
oLH	ovine LH
PID	pelvic inflammatory disease
STD	sexually transmitted disease
TSH	thyroid stimulating hormone
TT	tetanus toxoid
USAID	United States Agency for International Development
VILCI	Vaccine for Induced Local Cell Mediated Immunity
WHO	World Health Organization

PHOTOS

cover A hospital ward in Bombay where women rest after sterilisation.

page 11 Prototype of the Indian anti-oLH-hCG contraceptive. Three injections are needed to reach an effective threshold. The fourth vial is for a booster shot. All three primary doses are different.

page 21 The National Institute of Immunology, New Delhi; an assistant of Dr. Talwar's working in the lab.

page 36 The National Institute of Immunology, New Delhi; injection of Neem extract (described on page 31) into an anaesthetised rat.

page 40 A hospital in New Delhi; where women are being registered for Phase 2 clinical trials of immunological contraceptives.

page 50 A hospital in New Delhi; the doctor is injecting a woman with an immunological contraceptive.

page 59 Hospital in New Delhi; women are asked to participate in a clinical trial with immunological contraceptives during regular hours for consultations on contraception.

All photos were taken by Ulrike Schaz in India. We thank her for allowing us to use them.

GLOSSARY

Allergy Hypersensitivity against a specific antigen.

Antibody Proteins (called immunoglobulins) produced by the body during an immune response. Antibodies are specific for one antigen and can build an antigen-antibody complex, thus neutralising the antigen.

Antigen Any substance capable of reacting with antibodies.

Antigenic determinant Antigens often have several antigenic determinants, each of which can react with of specific antibodies.

Antigenic structure → Antigenic determinant

Auto-immune disease A pathological immune response which is directed against body tissue or processes instead of against a foreign substance. It can result in the destruction of tissue or interference with normal body functions.

Barrier methods Contraceptives which prevent pregnancies mechanically by preventing sperm from reaching the egg (condom, diaphragm, cervical cap).

Booster injection An injection which restimulates an immune response by renewing contact with the original antigen.

boosting → Booster injection

Birth control vaccine → Immunological contraceptive

Carrier Molecule that is linked to an antigenic determinant to make it more efficient in eliciting an immune response. If the antigenic determinant is part of a molecule normally present in the body, then the carrier is needed to make it appear foreign to the immune system.

Contraceptive vaccine → Immunological contraceptive

Corpus luteum A gland on the surface of the ovary which forms from the follicle after the egg cell leaves the ovary at ovulation. It is called the corpus luteum (yellow body) because of its colour. The corpus luteum secretes the hormone progesterone to prepare the uterus for implantation of the fertilised egg. If conception does not occur, the corpus luteum degenerates.

Cross reaction Antibodies against a specific antigen sometimes react also with other substances that have a sufficient similarity in antigenic structure.

Depo Provera® Injectable contraceptive consisting of a synthetic form of the hormone progesterone (medroxyprogesterone acetate) which prevents conception for three months.

Failure rate The number of pregnancies due to contraceptive failure per 100 women per year of contraceptive use (or per 1200 menstrual cycles of use). The failure rate may reflect both method failures, i.e. failures intrinsic to the method, and/or user failures, i.e. incorrect use of contraceptives resulting in pregnancies.

Follicle Fluid filled bubble in the ovary consisting of ovum, covering, and supporting cells that ripens for ovulation. The follicle ruptures at ovulation and releases the ovum. The supporting cells left behind form the corpus luteum.

FSH **F**ollicle **S**timulating **H**ormone. FSH is a hormone released by the pituitary gland, at the base of the brain, which stimulates together with LH the maturation of an egg in women in preparation for ovulation. In men, FSH stimulates the production and maturation of sperm.

GnRH **G**onadotrophin **R**eleasing **H**ormone. GnRH is released by the hypothalamus (part of the brain) which in turn stimulates the pituitary gland to release FSH and LH. These hormones are called gonadotrophins because they affect the gonads (ovaries and testes).

Gonads Reproductive organs: the ovaries which store eggs in women and the testes, which produce sperm in men.

HCG **H**uman **C**horionic **G**onadotrophin. HCG is released by the fertilised egg cell soon after fertilisation and continues to be produced by the placenta. It stimulates the corpus luteum in the ovary to continue to produce progesterone.

Hormonal contraceptives Contraceptive methods relying on synthetic forms of the hormones oestrogen and progesterone to prevent pregnancies (oral contraceptives, → injectables, → Norplant®, L-→ IUD).

Immune response The body's way of protecting itself against infection and foreign substances. A variety of specific and non-specific reactions that are triggered after contact with an antigen (e.g. virus, bacteria, toxin etc.). A primary immune response follows the first contact with an antigen; secondary immune response follows second and further contact with the same antigen. Secondary immune responses involve a different type of antibodies, have a shorter lag-phase and are much more efficient.

Immune tolerance Lack of immune response against a substance. Special type of tolerance: self-tolerance.

Immunisation The process of making a person immune against a specific micro-organism or toxin. There are two types of immunisation:

Active immunisation: The micro-organism or its toxin is altered in a way which makes it still function as an antigen, but does not lead to the outbreak of disease. The body produces antibodies and memory cells in response to these manipulated germ, leading to secondary immune responses against the natural germ.

Immunisation *continued*

Passive immunisation: Antibodies against a micro-organism or its toxin that have been extracted from another organism, such as sheep or rabbit, are injected into a person. Since these antibodies are produced externally, the body has no memory cells which can continue to produce them. After they are metabolised, the protection is gone. This vaccination is only for short-term immune protection.

Immunological contraceptives Contraceptive methods currently under development, which rely on an auto-immune reaction against reproductive substances. Several types of immunological contraceptives are being researched for men and women. Synonyms: birth control vaccine, contraceptive vaccine.

Immunogen → Antigen.

Immunopotentiators Substances that are added to vaccines to help stimulate an immune response.

Implants contraceptive implants; → Norplant®.

Injectables Contraceptive injections of synthetic hormones. Those currently in use consist of synthetic forms of the hormone progesterone which have a contraceptive effect for one month (NET-EN) to three months (Depo Provera®). Combined oestrogen/progesterone injectables are also being developed.

Intra-uterine device A small plastic or metal device which is inserted into the uterus to prevent pregnancy. A variety of forms and types of IUDs exist. Some IUDs are inert, others release copper or a synthetic form of the hormone progesterone (L-IUD).

IUD → Intra-uterine device

Lag period The period of time following immunisation in which an immune reaction hasn't yet reached an effective threshold.

LH **L**uteinising **H**ormone. LH is a hormone secreted by the pituitary gland at the base of the brain, which stimulates ovulation in women and production of testosterone in men.

NET-EN An injectable contraceptive consisting of a synthetic form of the hormone progesterone (norethisterone enanthate), which prevents pregnancies for two months.

Norplant® A contraceptive consisting of six silicone capsules which are implanted under the skin of a woman's arm. They are filled with a synthetic form of the hormone progesterone (levonorgestrel), which is slowly released, and they are effective for a period of five years. Minor surgery is required for insertion and removal of the capsules.

Self-tolerance The mechanisms by which body constituents avoid beeing attacked by the immune system.

Zona pellucida Thin layer around the egg cell.

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Judith Richter, born in 1954 in Germany, is a trained pharmacist and holds an MA. in Development Studies of the *Institute of Social Studies* in The Hague, the Netherlands. She has lived and worked in Switzerland, Thailand and the Netherlands. She lived in Thailand for over four years, working first as a lecturer in community pharmacy at *Khon Kaen University* and later as a researcher and information officer for a Bangkok based consumer protection group called the *Drug Information for Action Centre*. Together with her colleagues she began research on the administration of Norplant® in Thailand. She was invited to participate in two meetings on immunological contraceptives held by *WHO's Special Programme on Research, Development, and Training in Human Reproduction* (1989, 1992) as a consumer representative, and has been researching the development of immunological contraceptives for the past two years. Presently, she lives and works as a freelance researcher in The Hague, the Netherlands.

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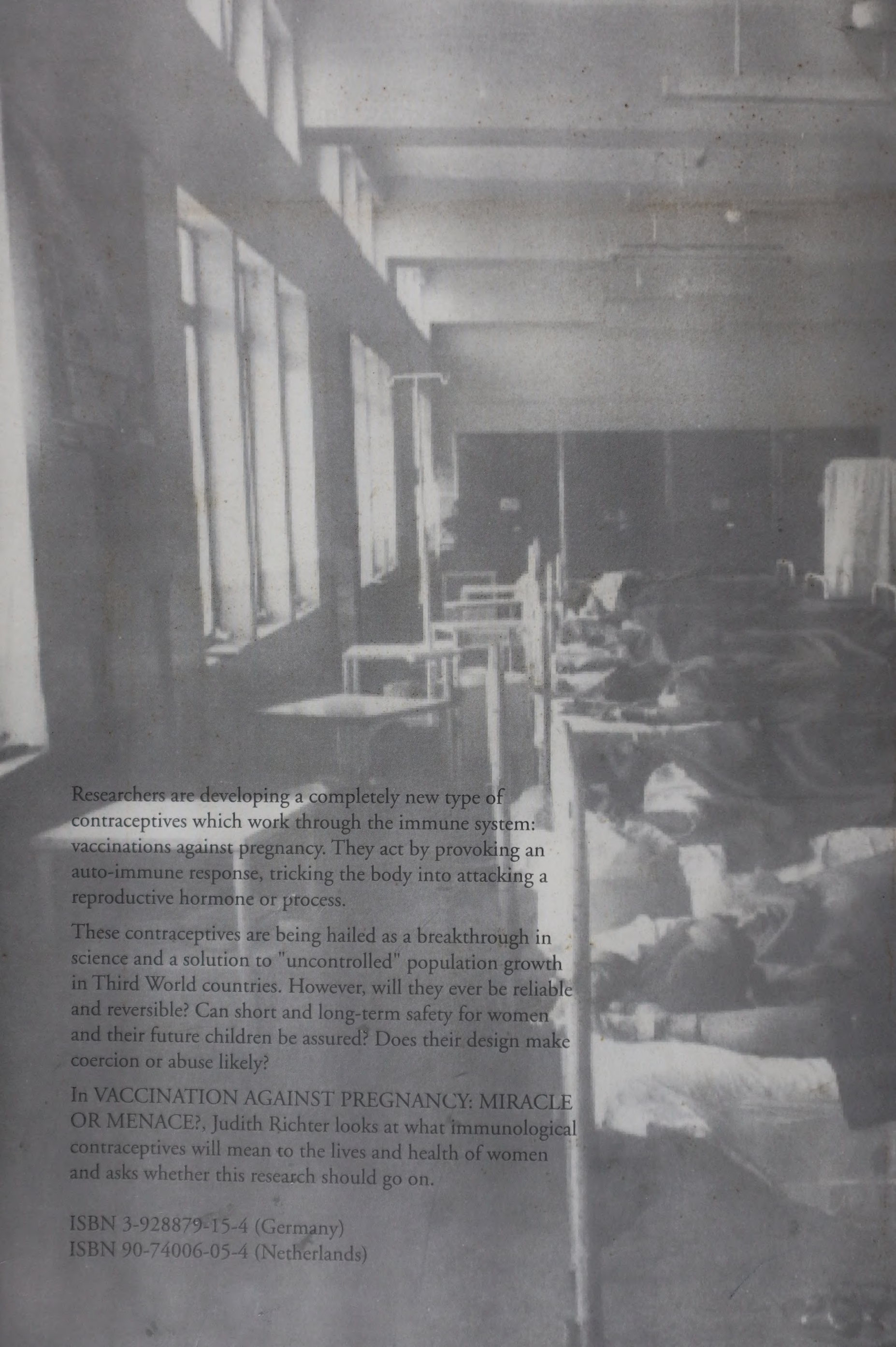

Researchers are developing a completely new type of contraceptives which work through the immune system: vaccinations against pregnancy. They act by provoking an auto-immune response, tricking the body into attacking a reproductive hormone or process.

These contraceptives are being hailed as a breakthrough in science and a solution to "uncontrolled" population growth in Third World countries. However, will they ever be reliable and reversible? Can short and long-term safety for women and their future children be assured? Does their design make coercion or abuse likely?

In VACCINATION AGAINST PREGNANCY: MIRACLE OR MENACE?, Judith Richter looks at what immunological contraceptives will mean to the lives and health of women and asks whether this research should go on.

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